ORCID

Susanna Ranta http://orcid.org/0000-0001-7854-0371

Helena Hägglöf[1]
Maria Magnusson[2,3,4]
Pia Petrini[1,4]
Tony Frisk[1,4]
Susanna Ranta[1,4]

[1]*Department of Women's and Children's Health, Karolinska Institutet, Stockholm, Sweden*
[2]*Department of Pediatrics, CLINTEC, Stockholm, Sweden*
[3]*Clinical Chemistry and Blood Coagulation Research, MMK, Karolinska Institutet, Stockholm, Sweden*
[4]*Pediatric Coagulation Unit, Karolinska University Hospital Stockholm, Stockholm, Sweden*

Correspondence: *Susanna Ranta, Karolinska University Hospital, A10:03, Eugeniavägen 3 A, 171 76 Stockholm, Sweden (susanna.ranta@ki.se).*

REFERENCES

1. Franchini M, Coppola A, Tagliaferri A, Lippi G. FEIBA versus NovoSeven in hemophilia patients with inhibitors. *Semin Thromb Hemost*. 2013;39(7):772-778.
2. Takedani H, Shima M, Horikoshi Y, et al. Ten-year experience of recombinant activated factor VII use in surgical patients with congenital haemophilia with inhibitors or acquired haemophilia Japan. *Haemophilia*. 2015;21(3):374-379.
3. Hoffman M, Dargaud Y. Mechanisms and monitoring of bypassing agent therapy. *J Thromb Haemost*. 2012;10(8):1478-1485.
4. Brown SA, Barnes C, Curtin J, et al. How we use recombinant activated Factor VII in patients with haemophilia A or B complicated by inhibitors. Working group of hematology experts from Australia and New Zealand, Melbourne, April 2011. *Intern Med J*. 2012;42(11):1243-1250.
5. Villar A, Aronis S, Morfini M, et al. Pharmacokinetics of activated recombinant coagulation factor VII (NovoSeven) in children vs. adults with haemophilia A. *Haemophilia*. 2004;10(4):352-359.
6. Quintana-Molina M, Martínez-Bahamonde F, González-García E, et al. Surgery in haemophilic patients with inhibitor: 20 years of experience. *Haemophilia*. 2004;10(Suppl 2):30-40.
7. Neunert CE, Miller KL, Journeycake JM, Buchanan GR. Implantable central venous access device procedures in haemophilia patients without an inhibitor: systematic review of the literature and institutional experience. *Haemophilia*. 2008;14(2):260-270.
8. Fonseca A, Nagel K, Decker K, et al. Central venous access device insertion and perioperative management of patients with severe haemophilia A: a local experience. *Blood Coagul Fibrinolysis*. 2016;27(2):156-159.
9. Ljung R, van den Berg M, Petrini P, et al. Port-A-Cath usage in children with haemophilia: experience of 53 cases. *Acta Paediatr*. 1998;87(10):1051-1054.
10. Bollard CM, Teague LR, Berry EW, Ockelford PA. The use of central venous catheters (portacaths) in children with haemophilia. *Haemophilia*. 2000;6(2):66-70.

Received: 2 March 2018 | Revised: 2 July 2018 | Accepted: 9 July 2018
DOI: 10.1111/hae.13598

Retrospective review of Acquired Haemophilia A from the largest Canadian Haemophilia treatment centre

Acquired haemophilia A (AHA) is a rare bleeding disorder characterized by the formation of neutralizing autoantibodies to factor VIII. Low factor VIII activity and the presence of inhibitory antibodies, usually detected by Bethesda assay, confirm the diagnosis.[1] About half of AHA cases are associated with underlying conditions such as malignancy, connective tissue diseases, drug exposures and pregnancy while the remainder is idiopathic.[2] There is a spectrum of clinical severity in AHA but many present with severe bleeding. In fact, the mortality rate from bleeding has been described at 4.5%.[3]

Treatment of AHA requires prohemostatic therapy and immunosuppressive therapy.[3-5] Prohemostatic therapy includes bypassing agents such as recombinant factor VIIa (rFVIIa), activated prothrombin complex concentrate (aPCC) and porcine factor VIII products (historically plasma-derived [pdpFVIII], currently recombinant [rpFVIII]). Inhibitor eradication is generally achieved via immunosuppressive therapy (IST); there is increasing concern regarding comparative risks and benefits of IST in this usually older patient population with competing comorbidities.[2]

Given its rarity, reports from collaborative European efforts such as the European Acquired Haemophilia registry (EACH-2)[3,6-8] and the GTH (Acquired Haemophilia Working Group of the German, Austrian and Swiss Thrombosis and Hemostasis Society) registry[9,10] have provided key insights. Toronto's St. Michael's Hospital (SMH) is the largest Canadian adult haemophilia treatment centre (HTC); we reviewed the clinical characteristics of AHA patients treated at SMH from 1990 to 2016. To our knowledge, this is the largest North American AHA patient series described to date.

Acquired haemophilia A patients were identified using a national haemophilia database, the Canadian Haemophilia Assessment and Resource Management Information System (CHARMS), and by reviewing the SMH transfusion database to ascertain which patients had received bypassing agents or porcine factor VIII products over these years. The clinical records of these patients were then reviewed to confirm an AHA diagnosis. Major bleeding and minor bleeding were defined by severity criteria defined by Schulman et al[11] Complete remission (CR) was defined by

[no notes on this page]

spontaneous factor VIII levels over 70% and an undetectable inhibitor titre. SAS 9.4 (SAS Institute Inc., Cary, NC USA) was used for all analyses. Box and whisker plots were generated using http://www.imathas.com/stattools/boxplot.html.

Eighty-eight bleeding episodes among 40 patients were identified. Our cohort's median age was 68 years, relatively consistent with other reports (median age 73.9 years in the EACH-2 registry; 74 years in the GTH registry; 64 years in an AHA meta-analysis) (3,10,13). Forty-five per cent of patients included in a meta-analysis were men[12] and 53% in the EACH-2 registry,[7] were men. We identified more male patients (68%), likely reflecting the lack of postpartum AHA cases identified, perhaps due to selection bias from identifying patients using the transfusion of prohemostatic therapy as postpartum cases may self-resolve without the need for prohemostatic intervention.

We found that 60% of initial bleeding episodes were of major severity, whereas subsequent bleeds were predominantly minor. We believe that this is due to prompt reinitiation of prohemostatic therapy in patients where the AHA diagnosis was already known. Overall, we identified a lower rate of severe bleeding (40%) compared to the EACH-2 (70%)[7]; however, the bleeding episodes reported in the EACH-2 included initial bleeding episodes only. Therefore, we reproduced the finding that the majority of initial bleeding episodes were severe in nature.

We found a nearly equal frequency of mucocutaneous, subcutaneous and intramuscular bleeding (33%-34%) and only one episode of intra-articular bleeding. We identified seven malignancy cases, and the associations in our cohort included oesophageal, lung and colon cancer, as well as chronic lymphocytic leukemia. Most of the plausible drug-related cases that we found were related to antibiotics and antiviral agents; again similar to the EACH-2 registry.[7] In 63% of our subjects, we did not find a secondary cause, similar to the findings of the United Kingdom[13] and GTH registry studies,[9] but higher than in the EACH-2 registry (51.9%)[7] and a meta-analysis of AHA cases (57.7%).[12]

Bypassing agents were used in 74% of all bleeding episodes, higher than the reported 64% use of these agents for bleeding episodes in the EACH-2.[3] Similar to EACH-2, the most commonly used bypassing agent in our patients was rFVIIa (56%), whether used alone or in combination with other agents. APCC was the next most commonly used bypassing agent (28%). Porcine factor VIII, either plasma derived or recombinant, was used in 13 bleeding episodes (13/88, 15%). The most commonly used supportive transfusion therapy was packed red blood cells; used in 41% of bleeding episodes.

We present data on dosing and infusion frequency of prohemostatic therapy that has not previously been described in such detail (Figure 1 and Table 1). The median doses of rFVIIa and aPCC are in the range of doses typically suggested for the management of severe bleeding with bypassing agents.[14,15] The median doses we found for rFVIIa are similar to those reported in the EACH-2 registry,[3] with a higher median dose and range for aPCC. Furthermore, there was decreased frequency of infusions of rFVIIa, aPCC and pdpFVIII after the first 48 hours, suggesting achievement of hemostatic control within this time period.

The box and whisker plots in Figure 1 demonstrate the frequency of infusions of the various bypassing agents in the first 48 hours and subsequent to that. A median of 4.5 infusions (IQR 2-6, range 1-9) of rFVIIa was used in the first 48 hours and thereafter declined to 3 (IQR 2.3-4, range 1-5). A similar trend of decreasing utilization after the first 48 hours was seen for aPCC and pdpFVIII. Only two patients were treated with rpFVIII, including one patient who required 26 doses of this therapy spread over 2 months.

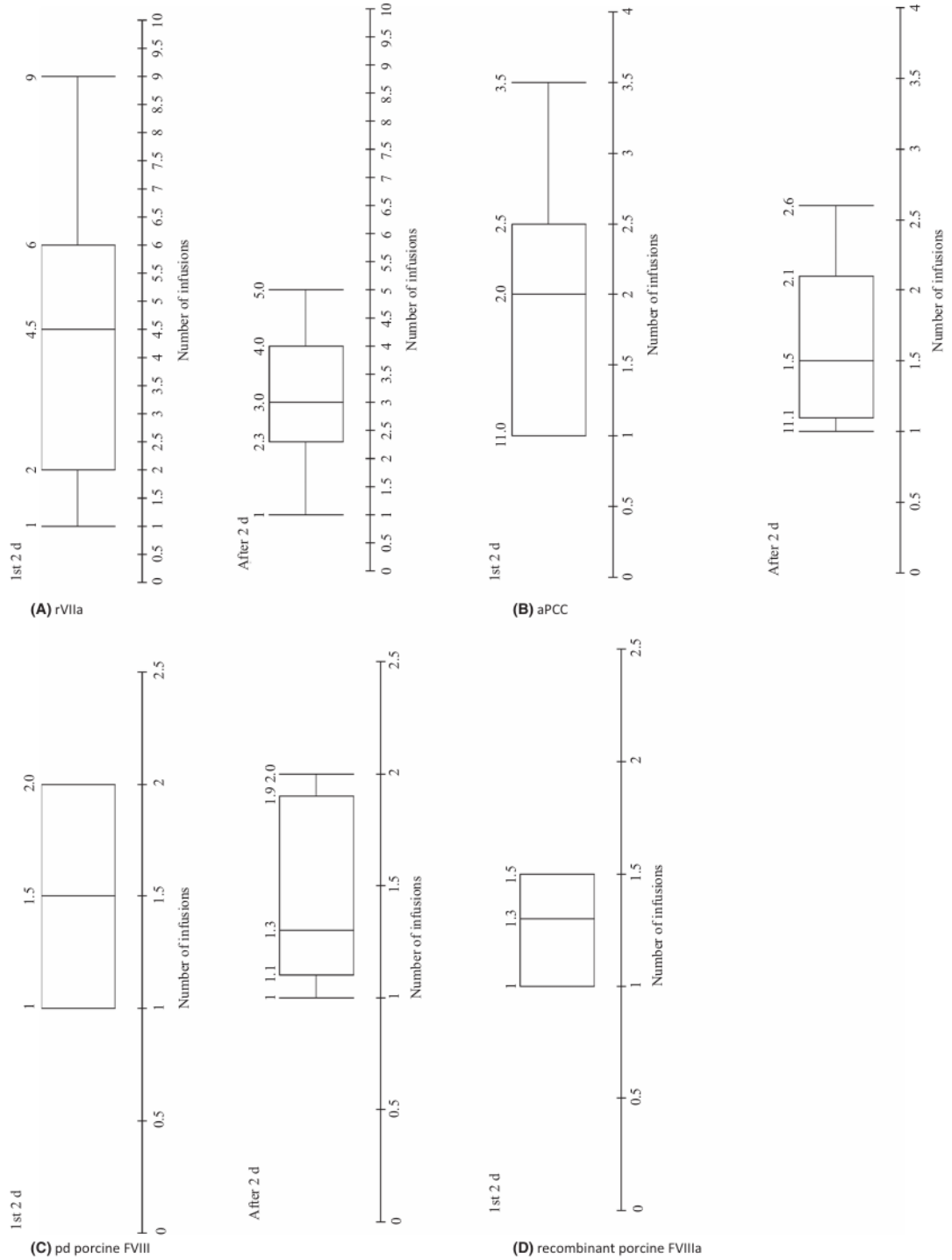
Porcine-derived FVIII, either recombinant or plasma derived, was used in 15% of bleeding episodes. PdpFVIII was used in 11 bleeding episodes before 2004, as it was withdrawn from the market that year due to concerns about viral safety. RpFVIII became licensed for use by Health Canada in October 2015 and was used in two patients in our cohort. One of these two patients had excessive bleeding not responding to traditional bypassing therapy and the second had disseminated intravascular coagulation secondary to bypassing therapy. Human factor VIII replacement products such as pd-VWF:FVIII and rFVIII were used in the management of two bleeding episodes, one of which had a confirmed low titre inhibitor.

All patients were treated with IST with a corticosteroid backbone. The most commonly used first-line regimen was a combination of steroid and cyclophosphamide (60% of patients). Only three patients were treated with corticosteroid and rituximab. Rarely, other agents such as vincristine, intravenous immunoglobulin (IVIG) and azathioprine were used in conjunction with corticosteroids. Second- and third-line IST regimens were required in 55% of the patients. Corticosteroid alone was the most commonly used IST in this context, and when used in combination with another IST, cyclophosphamide or rituximab was most commonly used. Complete remissions were documented in 73% of patients at some point during their disease course. Of those who did not achieve CR, the majority were lost to follow-up. In aggregate, 18 patients were lost to follow-up over time. We are aware of two deaths, both from causes unrelated to AHA.

Hospital admissions were required for 62 (70%) of all bleeding episodes, occurring in 87.5% of patients (n = 35). 12.5% of the bleeding episodes required critical care admission, and 40% of patients had

FIGURE 1 Usage of bypassing agents in first 48 h vs after first 48 h of bleeding episode. The box and whisker plots depict the median number of infusions for each agent during each time frame (first 48 vs after 48 h of presentation) with the interquartile ranges and overall range for (A) recombinant factor VIIa, (B) activated prothrombin complex concentrate, (C) porcine plasma-derived factor VIII and (D) porcine recombinant factor VIII. [a]A diagram was not generated for the after 48 h of presentation for porcine recombinant factor VIII as only one patient was treated with this agent after 48 h of presentation. This patient received infusions for up to 26 days for a very severe bleeding episode, and the mean number of infusions required after the first 48 h for this patient was two infusions per day until day 26

1. **Corticosteroid alone was the most commonly used IST in this con- text, and when used in combination...**
Anchor Name: mortalite
[Agency Turkey sibel.cakan@pitstop.com.tr]



[no notes on this page]

TABLE 1 Median doses of hemostatic therapies, by bleeding episode, used in AHA cohort

Therapy	Median (interquartile range)	Range
rFVIIa[a]		
Dose (mg)	6.8 (6.0-7.2)	4.8-9.6
Dose per weight (μg/kg)	90.9 (90.0-96.0)	74.6-158.7
aPCC[b]		
Dose (IU)	4231.3 (3865.5-5199.8)	2750.6-6048.0
Dose per weight (IU/kg)	72.8 (60.5-78.5)	45.2-94.5
Porcine pdFVIII[c]		
Dose (IU)	5932.5 (4900.0-6346.7)	3600.0-8015.0
Dose per weight (IU/kg)	88.5 (62.0-95.4)	44.8-121.4
Porcine rFVIII[d]		
Dose (IU)	7048.8 (4827.6-9270.0)	4827.6-9270.0
Dose per weight (IU/kg)	157.9 (70.6-245.2)	70.6-245.2

[a]Dose information was available for 33/49 episodes where rFVIIa was used. Patient weight information was available for 31/49 episodes. rFVIIa, recombinant factor VIIa.
[b]Dose information was available for 21/25 episodes where aPCC was used. aPCC, activated prothrombin complex concentrate.
[c]Dose information was available for 11 bleeding episodes. Porcine pdFVIII, porcine plasma-derived factor VIII.
[d]Dose information available for both episodes in which recombinant porcine FVIII was used. Porcine rFVIII, porcine recombinant factor VIII.

TABLE 2 Frequency of adverse events seen in AHA patients by organ system that could plausibly be related to IST

Complication by organ system	Frequency (n = 40 patients)
Cardiovascular	3 (7.5%)
Gastrointestinal	5 (12.5%)
Neuropsychiatric	15 (37.5%)
Genitourinary	2 (5%)
Metabolic	8 (20%)
Haematologic	10 (25%)
Musculoskeletal/dermatologic	6 (15%)
Infection	11 (27.5%)

Most patients with adverse events had multiple events, and 28 patients (70% of cohort) had at least one adverse event. Events seen for each system are as follows. Cardiovascular: congestive heart failure, atrial fibrillation and demand ischemia. Gastrointestinal: transaminitis and vomiting. Neuropsychiatric: fatigue, insomnia, dizziness, mood changes, tremor, confusion, headache and paresthesias. Genitourinary: acute kidney injury and amenorrhea. Metabolic: hyperphagia, weight gain, hyperglycemia and overt diabetes. Hematologic: anemia, leukopenia and hypogammaglobulinemia. Musculoskeletal/dermatologic: hyperhidrosis, acne, alopecia, muscle weakness, dry skin and peripheral rash. Infectious: clostridium difficile diarrhea, intra-abdominal sepsis, urinary tract infection, palmar warts, respiratory infections, yeast infections and aspergillus infection.

more than one hospital admission. Hospital length of stay data could be obtained for 56 (64%) of the bleeding episodes and for those, the median length of stay was 11 days (IQR 6-24 days). These data emphasize the high intensity of healthcare utilization for AHA bleeding episodes and the need to optimize strategies to facilitate early diagnosis and efficacious management of AHA-related bleeding. Seventy per cent of patients in this study had documentation of significant adverse events that are plausibly related to IST (Table 2), some of which required de novo hospitalization (intra-abdominal sepsis), increased length of stay (uncontrolled diabetes mellitus) or additional therapies.

In conclusion, we have reviewed the largest North American AHA patient series published to date, observing similar clinical characteristics and therapies to European registry studies. Our findings reflect the high healthcare utilization frequently required in AHA, promise of rpFVIII for refractory bleeding, and significant toxicities of IST. We believe AHA research and care should focus on minimization of iatrogenic harm and study of novel, less toxic IST regimens in this vulnerable patient population.

AUTHOR CONTRIBUTION

M. Sholzberg and J. Jayakar conducted the literature review and conceived the study design. N. O'Neill and M. Yan collected data. R. Nisenbaum, J. Jayakar and M. Sholzberg analysed and interpreted the data. J. Jayakar and M. Sholzberg created the initial manuscript and figures. J. Teitel, M. Garvey, J. Jayakar and M. Sholzberg critically revised the manuscript and all authors were involved in the review and approval of the manuscript.

DISCLOSURES

Dr. Sholzberg has acted as a paid consultant to Shire and NovoNordisk. She has received unrestricted research support from Shire for this project.

ORCID

Jai P. Jayakar http://orcid.org/0000-0003-2265-5430
Michelle Sholzberg http://orcid.org/0000-0003-1220-0301

Jai P. Jayakar[1]
Natalya O'Neill[2]
Marie Yan[3]
Rosane Nisenbaum[4]
Marie B. Garvey[1]
Jerome Teitel[2]
Michelle Sholzberg[2,5]

[1]*Division of Hematology, Department of Medicine, University of Toronto, Toronto, Ontario, Canada*
[2]*Division of Hematology/Oncology, Department of Medicine, St. Michael's Hospital, University of Toronto, Toronto, Ontario, Canada*
[3]*Department of Medicine, University of Toronto, Toronto, Ontario, Canada*

[no notes on this page]

[4]Centre for Research on Inner City Health, Li Ka Shing Knowledge Institute, St Michael's Hospital, Dalla Lana School of Public Health, University of Toronto, Toronto, Ontario, Canada
[5]Department of Laboratory Medicine and Pathobiology, St. Michael's Hospital, University of Toronto, Toronto, Ontario, Canada

Correspondence: Michelle Sholzberg, St Michael's Hospital, Room 2-007G Core Lab, Cardinal Carter Wing, 30 Bond Street, Toronto ON M5B 1W8, Canada (sholzbergm@smh.ca).

REFERENCES

1. Tiede A, Werwitzke S, Scharf RE. Laboratory diagnosis of acquired hemophilia A: limitations, consequences, and challenges. *Semin Thromb Hemost*. 2014;40:803-811.
2. Baudo F, de Cataldo F. The problem of acquired hemophilia. *Blood*. 2015;125:1052-1053.
3. Baudo F, Collins P, Huth-Kuehne A, et al. Management of bleeding in acquired hemophilia A: results from the European Acquired Haemophilia (EACH2) Registry. *Blood*. 2012;120:39-46.
4. Collins PW. Management of acquired haemophilia A. *J Thromb Haemost*. 2011;9:226-235.
5. Tiede A, Scharf R, Dobbelstein C, Werwitzke S. Management of acquired haemophilia A. *Hämostaseologie*. 2015;35:311-318.
6. Collins P, Baudo F, Knoebl P, et al. Immunosuppression for acquired hemophilia A: results from the European Acquired Haemophilia Registry (EACH2). *Blood*. 2012;120:47-55.
7. Knoebl P, Marco P, Baudo F, et al. Demographic and clinical data in acquired hemophilia A: results from the European Acquired Haemophilia Registry (EACH2). *J Thromb Haemost*. 2012;10:622-631.
8. Tengborn L, Baudo F, Huth-Kühne A, et al. Pregnancy-associated acquired haemophilia A: results from the European Acquired Haemophilia (EACH2) registry. *BJOG*. 2012;119:1529-1537.
9. Tiede A, Klamroth R, Scharf RE, et al. Prognostic factors for remission of and survival in acquired hemophilia A (AHA): results from the GTH-AH 01/2010 study. *Blood*. 2015;125:1091-1097.
10. Tiede A, Hofbauer CJ, Werwitzke S, et al. Anti-factor VIII IgA as a potential marker of poor prognosis in acquired hemophilia A: results from the GTH-AH 01/2010 Study. *Blood*. 2016;127:2289-2297.
11. Schulman S, Kearon C; Subcommittee on Control of Anticoagulation of the S, Standardization Committee of the International Society on T, Haemostasis. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. *J Thromb Haemost*. 2005;3:692-694. https://doi.org/10.1111/j.1538-7836.2005.01204.x.
12. Delgado J, Jimenez-Yuste V, Hernandez-Navarro F, Villar A. Acquired haemophilia: review and meta-analysis focused on therapy and prognostic factors. *Br J Haematol*. 2003;121:21-35.
13. Collins PW, Hirsch S, Baglin TP, et al. Acquired hemophilia A in the United Kingdom: a 2-year national surveillance study by the United Kingdom Haemophilia Centre Doctors' Organisation. *Blood*. 2007;109:1870-1877.
14. NovoNordisk-Canada. NiaStase RT (activated recombinant factor VIIa) product monograph. 2015. http://www.novonordisk.ca/content/dam/Canada/AFFILIATE/www-novonordisk-ca/OurProducts/PDF/niastase-product-monograph.pdf. Accessed June 2017.
15. Baxter-Healthcare-Corporation. FEIBA NF product monograph. 2011. http://www.feiba.com/us/forms/feiba_nf_pi.pdf. Accessed June 2017.

Received: 14 June 2018 | Revised: 11 July 2018 | Accepted: 16 July 2018
DOI: 10.1111/hae.13601

Efficacy and safety of low-dose prophylaxis of highly purified plasma-derived factor VIII concentrate produced by the National Blood Centre, Thai Red Cross Society

The National Blood Centre, Thai Red Cross Society (TRCS) has an essential task in preparing adequate and safe blood and blood components for replacement therapy among patients in Thailand. The pilot project of producing albumin has been established. The remaining plasma from TRCS was sent to the Green Cross Corporation (GCC), The Republic of Korea for plasma contract fractionation programme during the previous 14 years from 1999 to 2013. In 2010, the cabinet of Thai ministers agreed to set up a plasma fractionation centre to produce albumin, intravenous immunoglobulin (IVIG) and highly purified factor VIII concentrate with the aim of achieving self-reliance and reduced importation of foreign products. Her Royal Highness Princess Maha Chakri Sirindhorn offered her patronage to the centre as evident by its name, "The Thai Red Cross Plasma Fractionation Centre, Princess Maha Chakri Sirindhorn 5th Cycle Birthday Anniversary Celebration 2nd April, 2015." The transfer of technology from the GCC, Korea has been completed. The fractionation centre with its 135 personnel is located in Chonburi Province, about 81 km from Bangkok. The centre occupies 9850 m^2 across more than five acres and consists of eight sections, namely the administration building, a production building (including quality assurance and quality control), a utility building, an animal laboratory, an alcohol regeneration system, a waste storage, a waste water treatment plant and a city water tank with pump. The construction and machine installation were completed in 2 years, from April 2013 to May 2015. The three consecutive commercial trial batches of Albumin 20 TRTC (20% albumin), Immunoglobulin 5 TRTC (5% IVIG) and Factor VIII TRTC (highly purified factor VIII concentrates) were produced from July to October 2015.

The highly purified factor VIII concentrate was prepared from voluntary blood donations which were negative for VDRL, anti-HIV-1/2, HIV-antigen, HBsAg, anti-HCV both from serological and nucleic acid amplification tests (NAT). The majority of plasma (97%) comprised

[no notes on this page]