Low incidence of factor VIII inhibitors in previously untreated patients with severe haemophilia A treated with octanate®: Final report from a prospective study

A. Klukowska1 | V. Komrska2 | V. Vdovin3 | A. Pavlova4 | M. Jansen5 | S. Lowndes6 | L. Belyanskaya6 | O. Walter6 | P. Laguna1

1Department of Paediatrics, Haematology and Oncology, Medical University of Warsaw, Warsaw, Poland
2Motol University Hospital, Prague, Czech Republic
3Morozovskaya Children’s Hospital, Moscow, Russia
4Institute of Experimental Haematology and Transfusion Medicine, University Clinic, Bonn, Germany
5Octapharma, Vienna, Austria
6Octapharma AG, Lachen, Switzerland

Introduction: Octanate® is a human, plasma-derived, von Willebrand factor-stabilized coagulation factor VIII (FVIII) concentrate with demonstrated haemostatic efficacy in previously treated patients with haemophilia A.

Aim: This prospective, open-label study aimed to assess the immunogenicity of octanate® in previously untreated patients (PUPs).

Methods: The study monitored development of FVIII inhibitors in 51 PUPs. Tolerability, viral safety, FVIII recovery and efficacy of octanate® for the prevention and treatment of bleeds and in surgical procedures were also assessed.

Results: Five (9.8%) of the 51 patients developed inhibitors during the study, 4 of which (7.8%) were high titre. Three inhibitor cases (5.9%) were considered clinically relevant; 2 were transient inhibitors that disappeared during regular octanate® treatment without a change in dose or treatment frequency. Amongst 45 patients with FVIII:C <1% at baseline and who received ≥20 exposure days (EDs) or had <20 EDs but developed an inhibitor, inhibitor incidence was 11.1% (6.7% clinically relevant). All clinically relevant inhibitors developed within 20 EDs of on-demand treatment. No inhibitors developed in PUPs receiving prophylaxis. All patients who developed inhibitors had either intron 22 inversions or large deletions. Irrespective of the reason for administration, haemostatic efficacy was rated as “excellent” in 99.6% of all infusions (4700 of 4717 infusions), and no complications were reported in 23 surgical procedures. Mean incremental in vivo recovery was 2.0%/IU/kg (±0.7) and 1.9%/IU/kg (±0.5) for the first and second assessments, respectively. Tolerability was rated “very good” in 99.9% of infusions.

Conclusion: In PUPs with severe haemophilia A, octanate® demonstrated haemostatic efficacy with a low rate of inhibitor development.

KEYWORDS
factor VIII inhibitors, haemophilia A, octanate®, plasma-derived factor VIII, previously untreated patients

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

© 2018 The Authors. Haemophilia Published by John Wiley & Sons Ltd.
Patients with haemophilia A (HA) are deficient in coagulation factor VIII (FVIII), predisposing them to recurrent bleeds, particularly into joints and muscles, culminating in debilitating arthropathy and long-term morbidity.\(^1\рин Administration of FVIII, either plasma-derived or recombinant (pd-FVIII or rFVIII), restores clotting capacity and limits uncontrolled bleeding. Administered prophylactically or on demand, FVIII has been shown to be effective and well tolerated. However, development of FVIII inhibitors remains a serious complication in replacement therapy with major adverse implications on bleeding rates, morbidity, mortality, quality of life and treatment costs.\(^2\) Reduction in the overall immunogenic challenge of replacement factor therapy remains one of the main unmet needs in HA.

Previously untreated patients (PUPs) with HA are at greatest risk of inhibitor development. Approximately 35% develop inhibitors, of which up to 70% are high-titre inhibitors (≥5 Bethesda Unit (BU)/mL).\(^6\) Inhibitors in PUPs with severe HA usually occur within the first 50 exposure days (EDs), with a median around 10-15 EDs.\(^6\) Data from the study showed cumulative inhibitor incidence of 26.8% in PUPs treated with pdFVIII-containing von Willebrand factor (VWF) and 44.5% in those treated with rFVIIIIs derived from hamster cell lines; the majority (90%) of inhibitors developed within the first 20 EDs.\(^6\)

FVIII inhibitor development is considered to be a multifactorial event. Patient-related risk factors include the type of F8 gene mutation, age at first exposure, ethnicity and a family history of inhibitors.\(^3\) The type of treatment approach (prophylactic or on demand after 20 EDs), intensity of FVIII exposure (eg during surgery), type of FVIII product (plasma-derived or different generations of recombinant FVIII) and VWF content of the FVIII product have been also identified as possible risk factors for inhibitor development.\(^4\) The European Medicines Agency (EMA) speculates that the cell origin (human or animal) of rFVIII products could influence immunogenicity,\(^8\) although definitive evidence of an increased inhibitor risk with rFVIII derived from animal cell lines has not been published.

In contrast to PUPs, only around 1% of previously treated patients (PTPs) develop inhibitors.\(^9\) Therefore, to assess the immunogenic potential of different FVIII products, it is essential to perform sufficiently large immunogenicity studies in PUPs.

Octanate\(^\circledast\) (Octapharma AG, Lachen, Switzerland) is a human, plasma-derived, high purity, coagulation FVIII concentrate stabilized with VWF in a ratio of ~0.4 (VWF:ristocetin cofactor activity/FVIII:coagulant activity [VWF:RCO/FVIII:CC]), such that all FVIII molecules could complex with VWF. There is evidence that VWF has a protective role against inhibitor development. The stability of infused FVIII depends on its native VWF-binding properties, which are dependent on the post-translational modifications (PTMs) of FVIII.\(^7\) FVIII undergoes extensive PTMs, which are species-specific and can thus differ between human and hamster cell-derived rFVIII products.\(^1\) Non-human epitopes potentially present in hamster cell-derived rFVIII products may have antigenic properties.\(^1\) Additionally, VWF may decrease FVIII immunogenicity due to epitope masking and protection of FVIII from endocytosis by antigen-presenting cells.\(^1\)

Octanate\(^\circledast\) has been marketed since 1998 and is approved in more than 85 countries for the treatment and prophylaxis of bleeding in patients with HA, including for surgical procedures. In 5 prospective clinical studies in a total of 77 PTPs, only one patient developed an inhibitor; however, this patient had frequently received an alternative FVIII product, and a relationship with octanate\(^\circledast\) could not be ascertained. Recently, a high success rate was demonstrated with octanate\(^\circledast\) in immune tolerance induction (ITI) therapy in a cohort of 48 HA patients with FVIII inhibitors and poor prognosis\(^2\); octanate\(^\circledast\) is now approved for ITI in 40 countries. Considerable clinical experience exists with octanate\(^\circledast\), with >9.6 billion international units (IU) infused worldwide (as of April 2017) (Octapharma, data on file).

Here, we present the final results of a prospective study of octanate\(^\circledast\) in PUPs with severe HA. The primary objective of the study was to assess the immunogenicity of octanate\(^\circledast\). Secondary objectives were assessment of tolerability, viral safety and efficacy of octanate\(^\circledast\) for the prevention and treatment of bleeds and in surgical procedures.

2   MATERIALS AND METHODS

2.1  Patients and study design

This prospective, open-label, non-controlled, multinational, multicentre study of octanate\(^\circledast\) was conducted according to good clinical practice (GCP; EudraCT 2005-004435-22) and was initiated in accordance with EMA guidance on clinical studies required for FVIII replacement products at the time.\(^2\) The study was initiated in February 2000 and completed in January 2015. Patients had severe HA (FVIII coagulant activity [FVIII:C] <2%, as per the accepted definition of severe HA at the time\(^2\)) with no previous treatment with FVIII-containing products and no inhibitor activity (<0.6 BU). Informed consent was obtained from the patients’ parents or legal guardians. Exclusion criteria included any bleeding disorder other than severe HA, interferon therapy and participation in other clinical studies, either concurrently or within the 4 weeks prior to enrolment.

Each patient received octanate\(^\circledast\) as replacement therapy, either prophylactically or for treatment of bleeds, for a total of 100 EDs or 5 years, whichever came first. Octanate\(^\circledast\) dosing and frequency was dependent upon the clinical situation and the treatment policies at the individual study centres.

2.2  Study drug

Octanate\(^\circledast\) is supplied as a freeze-dried concentrate in vials containing 250, 500 or 1000 IU FVIII. The manufacturing process includes 2 validated virus-inactivation steps.

2.3  Clinical outcomes and laboratory parameters

Patients were tested for FVIII inhibitors at baseline, every 3 or 4 EDs until 20 EDs, and thereafter either every 10th ED or every 3 months, whichever came first. Testing was performed at a central laboratory using the Bethesda assay with Nijmegen modification. The cut-off for FVIII inhibitors was ≥0.6 BU. Blood samples were to be taken after a...
FVIII wash-out period of at least 3 or 4 days, ideally 7 days (especially if the presence of an inhibitor was suspected). FVIII recovery determinations and calculations of incremental in vivo recovery (IVR) were recommended but not mandatory due to blood collection restrictions in babies/toddlers. Where IVR was performed, it was preceded by a wash-out period of at least 48 hours, and a single bolus dose (25-30 IU/kg recommended) was administered. The type of F8 gene mutation was determined for each patient.

The following viral markers were measured at baseline and at 3-month intervals for 5 years, or until 100 EDs were reached: alanine aminotransferase, antibodies to human immunodeficiency virus 1 and 2, hepatitis A virus, hepatitis B virus, hepatitis B surface/antigen, hepatitis B core, hepatitis C virus and parvovirus B19 (including polymerase chain reaction [PCR] testing). Haemostatic efficacy was rated by the investigator (or parent or legal guardian for home-treatment) as "excellent," "good," "moderate" or "none." Tolerability was rated by the investigator (or by the parent or legal guardian for home-treatment) as "very good," "good," "satisfactory" or "unsatisfactory." All adverse events (AEs) experienced by patients were analysed based on MedDRA (version 17.1) terminology.

2.4 Statistical analyses and sample size

No sample size calculation was made for this study. The planned sample size of 50 patients complied with the recommended sample size of at least 20 PUPs recommended in the EMA guidelines available at the time of study initiation.21

The safety population included all patients who received at least one dose of octanate®. The efficacy population comprised patients who received octanate® and for whom data were collected post treatment. A surgery subpopulation was analysed separately (Figure 1). All efficacy analyses were repeated to exclude data after occurrence of the inhibitor from patients who started ITI treatment as increased treatment doses for these patients would bias the assessment of all efficacy parameters.

Statistical analyses were performed using the Statistical Analysis Software (SAS®) package (version 9.8, SAS Institute Inc. Cary, North Carolina, USA). Analyses were exploratory only and based upon a type I error probability of 0.05 with confidence interval calculations set at 95%.

3 RESULTS

3.1 Patients’ baseline characteristics

The safety population comprised 51 Caucasian male patients, all of whom were included in the efficacy population (Table 1). Surgical procedures (n = 28) were conducted in 20 patients. The median age of patients vaccinated prior to study, n (%)

| Characteristics                                      | Value     |
|-------------------------------------------------------|-----------|
| Age, months, median (range)                           | 7.7 (0.1-67.3) |
| Family history, n (%)                                 |           |
| HA                                                    | 27 (52.9) |
| HA with inhibitors to FVIII                            | 3 (5.9)   |
| Type of mutation, n (%)                               |           |
| Intron 22 inversion                                   | 27 (52.9) |
| Nonsense mutation                                     | 4 (7.8)   |
| Stop mutation                                         | 5 (9.8)   |
| Missense mutation                                     | 9 (17.7)  |
| Large deletion                                        | 3 (5.9)   |
| Splice site mutation                                  | 2 (3.9)   |
| Exon 14 polymorphism (c.3780 C>G)                     | 1 (2.0)   |
| F8 genotype, n (%)                                    |           |
| High-risk                                             | 41 (80.4) |
| Low-risk                                              | 9 (17.6)  |
| Null                                                  | 41 (80.4) |
| Non-null                                              | 9 (17.6)  |
| Patients vaccinated prior to study, n (%)             |           |
| Hepatitis A virus                                     | 0 (0)     |
| Hepatitis B virus                                     | 47 (92.2) |
| Blood group, n (%)                                    |           |
| A                                                     | 21 (41.2) |
| B                                                     | 10 (19.6) |
| AB                                                    | 4 (7.8)   |
| O                                                     | 15 (29.4) |

aAt study entry.

bNo clear causal mutation in the FVIII coding region.

cHigh-risk mutations: intron 22 inversions, intron 1 inversions, nonsense mutations, large deletions, splice site mutations; Low-risk mutations: missense mutations. Mutation in one patient could not be assessed for high/low risk.

dNull mutations: intron 22 inversions, intron 1 inversions, nonsense mutations, large deletions, stop mutations and splice site mutations; Non-null mutations: missense mutations. Mutation in one patient could not be assessed for null/non-null.

eBlood group was unknown for one patient.

TABLE 1 Baseline demographics and clinical characteristics of the safety population (N=51)
patients at study entry was 0.6 (range: 0.01-5.6) years. A family history of HA and FVIII inhibitors was reported in 27 (52.9%) and 3 (5.9%) patients, respectively. Forty-seven patients (92.2%) had FVIII:C <1%. High-risk/null mutations (including intron 22 inversions, nonsense/stop/splice site mutations and large deletions) were identified in 80.4% of patients (Table 1). One patient had no clear causal mutation in the FVIII coding region but had a polymorphism in exon 14 (c.3780 C>G).

3.2 | Dosing and exposure

Octanate® was administered to 51 patients, with a mean of 136.33 (±246.3) EDs and a mean dose of 38.4 (±28.6) IU/kg/ED. The total number of EDs was 6953. At study end, 40 (78.4%) patients had 100 or more EDs. Forty-six (90.2%) patients had exceeded 50 EDs and 2 (3.9%) had 20-49 EDs. Three patients (5.9%) had <20 EDs: one patient withdrew consent after 10 EDs; one was lost to follow-up after 3 EDs; and for one patient who developed an inhibitor, treatment was terminated due to completion of the study after 17 EDs.

Prophylaxis was the most common reason for treatment, accounting for 3027 EDs. ITI accounted for 1869 EDs, treatment of bleeds for 1817 EDs, surgical procedures for 149 EDs and IVR assessments for 106 EDs.

3.3 | Incidence of FVIII inhibitors

FVIII inhibitors were detected in 5 of 51 (9.8%) patients; 4 cases were high-titre inhibitors, 1 was a low-titre inhibitor (Table 2). Clinically relevant inhibitors (defined as at least 2 positive titres and a decrease in IVR of FVIII) were reported in 3 (5.9%) patients. Two patients had transient inhibitors that disappeared during regular octanate® treatment without a change in dose or treatment frequency and were considered clinically irrelevant. Of the 51 patients in the study, 4 had an FVIII:C level ≥1%, and 2 patients who did not develop inhibitors had <20 EDs. Excluding these patients, the incidence of inhibitor development was 11.1% (5/45) for all inhibitors, 8.9% (4/45) for high-titre inhibitors and 6.7% (3/45) for clinically relevant inhibitors.

| Patient | Type of inhibitor | Number of EDs prior to detection | Family history HA/inhibitors | F8 gene defect | Maximum inhibitor titre (BU) | Regimen at time of inhibitor detection | Clinically relevant |
|---------|------------------|---------------------------------|-----------------------------|---------------|----------------------------|--------------------------------------|-------------------|
| 1       | High responding  | 6                               | No/No                       | Large deletions of exons 7-12 | 328                       | On demand                            | Yes               |
| 2       | Transient (high responding) | 19                           | No/No                       | Intron 22 inversion              | 7                         | On demand                            | No                |
| 3       | High responding  | 3                               | Yes/Yes                     | Intron 22 inversion              | 445                       | On demand                            | Yes               |
| 4       | Transient (low responding) | 48                           | Yes/No                      | Intron 22 inversion              | 2.1                       | On demand                            | No                |
| 5       | High responding  | 11                              | No/No                       | Intron 22 inversion              | 29                        | On demand                            | Yes               |

BU, Bethesda units; ED, exposure day; FVIII, factor VIII; HA, haemophilia A.
All clinically relevant inhibitors were detected within the first 20 EDs. All the patients who developed inhibitors were receiving on-demand treatment and had major F8 gene defects, either intron 22 inversions (n = 4) or large deletions of exons 7-12 (n = 1). The patient who developed the highest inhibitor titre had a family history of inhibitors. No new inhibitors were detected in any patient beyond 50 EDs, and no new high-titre inhibitors were detected beyond 20 EDs.

3.4 | FVIII recovery

Although IVR determination was optional in this study, 44 of the 51 patients underwent at least one IVR assessment, 36 had a second and one had a third assessment. Notable levels of FVIII were evident in the blood at 15 minutes postinfusion and remained high at 1 hour (Figure 3).

Mean (±SD) incremental IVR was 2.0%/IU/kg (±0.7) for the first IVR assessment (n = 44) and 1.9%/IU/kg (±0.5) for the second assessment (n = 36).

3.5 | Haemostatic efficacy

Haemostatic efficacy was rated as "excellent" for 99.6%, "good" for 0.3% and "moderate" for 0.02% of all infusions (Table 3). The majority of bleeds (95.5%) resolved within 1 or 2 days of treatment (81.2% and 14.3%, respectively). All minor bleeds and the majority of moderate (95.0%) and severe bleeds (76.0%) resolved within 3 days of treatment. Efficacy for all but one of the 2611 prophylactic infusions was rated as "excellent" (one was rated as "good"), and efficacy for all IVR infusions with available efficacy ratings (n = 80/81) was rated as "excellent."

Twenty-three surgical procedures in 19 patients using octanate® as haemostatic cover were evaluated for efficacy. Five procedures in one patient undergoing ITI were excluded from analysis. Efficacy for all 201 infusions was rated as "excellent." Eighteen procedures were classed as minor (78.3%), whilst 5 (21.7%) were major. Mean (±SD) total dose per ED was 56.7 IU/kg (±15.8) for minor procedures and 59.2 IU/kg (±9.0) for major procedures, during a mean of 5.9 (±2.9) and 8.4 (±1.5) EDs, respectively. No FVIII inhibitors developed after major surgeries, and 2 patients who underwent minor surgeries developed transient inhibitors that resolved without changes to octanate® treatment. Major surgeries are summarized in Table 4. There was one case of intracranial haemorrhage, which was treated by craniotomy without further complications.

3.6 | Safety and tolerability

A total of 260 treatment-emergent AEs were recorded in 45 (88.2%) patients. AEs reported were typical for any paediatric or haemophilia
population monitored over a long period. Of the 260 AEs, 78 reported in 34 patients were serious adverse events (SAEs). Twenty-one AEs were considered probably or possibly related to octanate®: 16 cases of asymptomatic parvovirus B19 seroconversions and 5 cases of FVIII inhibitor development. These were classified as SAEs according to the study protocol.

The tolerability of octanate® was considered "very good" in the vast majority of the 8674 infusions (99.98%) and 2 (0.02%) were assessed as "good".

4 | DISCUSSION AND CONCLUSIONS

The immunogenicity and efficacy of octanate® were investigated in paediatric PUPs, and a low rate of inhibitor development was observed. In the 51 PUPs in this study, 5 (9.8%) patients developed inhibitors, 4 (7.8%) of which were high titre. Of these, only 3 (5.9%) were considered clinically relevant, all of which developed within the first 20 EDs after on-demand treatment. The other 2 patients developed transient inhibitors that disappeared during regular octanate® treatment without a change in dose or treatment frequency. Within the 45 patients who reached ≥20 EDs (or developed an inhibitor <20 EDs) and had FVIII:C <1% at baseline, the incidence of inhibitor development was 11.1%. This inhibitor incidence compares very favourably with historical reports of incidences of up to 45% in similar populations.

The influence of FVIII product type on inhibitor incidence has been intensely debated over the past decade. Some studies and meta-analyses have reported an increased inhibitor risk with rFVIII compared with pdFVIII, whereas other studies and meta-analyses reported no difference in inhibitor risk. In a retrospective study of 99 PUPs, no inhibitors were detected in 11 PUPs treated with wilate®, a pdFVIII concentrate containing FVIII and VWF in a physiological 1:1 ratio, and inhibitors were detected in 38% of PUPs treated with rFVIII concentrates derived from hamster cell lines.

Comparisons of inhibitor risk have been limited by the heterogeneity of study designs and patient populations. For example, the EPIC study attempted to confirm a reported inhibitor incidence of only 4% reported by Kurnik et al³⁰ with a weekly prophylaxis regimen and in fact found inhibitor development in 42% of patients. The small cohort size of studies reporting inhibitor development likely contributes to discrepancies and must be taken into account when attempting to make direct comparisons. A meta-analysis attempted to overcome some of these limitations by analysing data in 761 PUPs with severe or moderate haemophilia.³⁰ Unadjusted inhibitor rates were higher in patients treated with rFVIII compared with patients treated with pd-FVIII (40% vs 22%); however, this difference did not persist after adjustment for confounding factors.

More recently, the results of the first randomized controlled study to investigate the impact of FVIII types on inhibitor incidence were published. The SIPPET study compared inhibitor rates in PUPs treated with pdFVIII (n = 125) or hamster cell line-derived rFVIII (n = 126).³² By univariate Cox regression analysis, rFVIII was associated with an 87% higher risk of inhibitor development than pdFVIII (cumulative incidence 44.5% vs 26.8%; hazard ratio [HR] 1.87) and a 69% higher risk of developing high-titre inhibitors (cumulative incidence 28.4% vs 18.6%; HR: 1.69). The associations did not change substantially after adjustment for putative confounders.³³ It is important to note the large variation between the inhibitor rate reported in patients treated with pdFVIII in the SIPPET study (26.8%) and the rate reported in this study (11.1%) may be related to differences in patient populations studied. For example, the majority of patients enrolled in the SIPPET study were from Egypt, India and Iran, whereas patients enrolled in this study were exclusively Caucasian.

Mouse studies have demonstrated higher levels of FVIII inhibitors following administration of hamster cell-derived rFVIII products compared with pdFVIII, and pre-incubation of rFVIII with VWF has been shown to reduce rFVIII immunogenicity. This suggests that an underlying cause of product-related development of a FVIII immune response may lie in the VWF-binding affinity and the presence of antigenic epitopes in animal cell-derived rFVIII products.³³³³

A number of reports have suggested that the use of on-demand treatment is associated with a higher risk of inhibitor development than regular prophylaxis.³³ In this study, all 5 patients who developed inhibitors received on-demand treatment. Furthermore, a high intensity of FVIII exposure (≥150 IU/kg/wk) is considered a strong risk factor for inhibitor development in PUPs, especially during surgical coverage.³⁴ In this study, 2 patients developed transient inhibitors during surgery. Reported inhibitor rates may vary depending on the frequency of testing; in this study, patients were tested frequently for FVIII inhibitor development.

Certain mutation types, such as intron 22 inversions, have been associated with a substantially higher risk of inhibitor development.³⁵ Intron 22 inversions were observed in 52.9% (27/51) of patients in this study. Two of these 27 patients (7.4%) developed clinically relevant FVIII inhibitors.

| Patient | Description of surgery | Dose (IU/kg) | Outcome |
|---------|------------------------|-------------|---------|
| 01-20   | Hernia inguinalis bilateralis | 543.5 | No bleeding or complications |
| 01-33   | Haematoma evacuation by craniotomy | 722.2 | No complications |
| 01-34   | Hernia inguinalis | 500.0 | No bleeding |
| 01-42   | Orchiopexy | 370.4 | No bleeding or complications |
| 03-62   | Excision of left appendix testis | 375.6 | Excellent |

TABLE 4 Description, total dose and outcome of major surgical procedures
In this study, the mean incremental IVR of octanate® of 2.0%/IU/kg (±0.7) for the first assessment (n = 44) and 1.9%/IU/kg (±0.5) for the second assessment (n = 36) are slightly lower than the 2.4%/IU/kg observed for octanate® in adults, which is consistent with an expected lower IVR for children compared with adults. The values are consistent with values reported for other FVIII concentrates in previously treated paediatric patients. The haemostatic efficacy of octanate® was rated “excellent” in 99.6% of administrations, irrespective of the reason for administration. Most bleeds (95.5%) resolved within 1 or 2 days. Octanate® tolerability was rated “very good” in 99.9% of infusions. No deaths were reported, and few SAEs were deemed possibly or probably linked to octanate®, namely 16 asymptomatic parvovirus B19 seroconversions and development of FVIII inhibitors in 5 patients, which were reported as SAEs in accordance with the study protocol. Due to the high prevalence of parvovirus B19 within the community, it is not possible to definitively assign these seroconversions to treatment with octanate®.

Early and efficient prophylaxis is key to successful long-term management of patients with HA. The data reported here demonstrate that octanate® is associated with a low rate of inhibitor development in PUPs, including those undergoing surgical procedures. The data are consistent with previous findings in PTPs demonstrating that octanate® is an efficacious and well-tolerated human FVIII for the management of patients with HA.

ACKNOWLEDGEMENTS

This trial was sponsored by Octapharma AG (Lachen, Switzerland), who thank investigators for documenting and analysing the data, and trial personnel and patients for their participation. Medical writing support was provided by nspm ltd (Meggen, Switzerland) and funded by Octapharma AG.

AUTHOR CONTRIBUTIONS

A. Klukowska, V. Komrska, V. Vdovin, A. Pavlova and P. Laguna performed the research, provided reagents and analytical tools, collected, contributed and analysed the data, and also wrote and reviewed the manuscript. M. Jansen, S. Lowndes, L. Belyanskaya and O. Walter contributed to the statistical analysis, interpretation, writing, review and co-ordination of the manuscript. All authors provided input and approved the manuscript.

DISCLOSURES

A. Klukowska has participated in studies sponsored by Octapharma AG and has received speaker fees from Octapharma AG, Baxalta, Novo Nordisk and has had paid consultations for CSL Behring and Novo Nordisk. V. Komrska has participated in studies sponsored by Octapharma AG. V. Vdovin has participated in studies sponsored by Octapharma AG. A. Pavlova has participated in studies sponsored by Octapharma AG. M. Jansen is an employee of Octapharma Pharmazeutika Produktionsges. m.b.H., Vienna, Austria. S Lowndes, L. Belyanskaya and O. Walter are employees of Octapharma AG, Lachen, Switzerland. P. Laguna has participated in studies sponsored by Octapharma AG.

REFERENCES

1. Coppola A, Di Capua M, Di Minno MN, et al. Treatment of hemophilia: a review of current advances and ongoing issues. J Blood Med. 2010;1:183-195.
2. Roosendaal G, Lafeber FP. Pathogenesis of haemophilic arthropathy. Haemophilia. 2006;12(Suppl 3):117-121.
3. Coppola A, Santoro C, Tagliaferri A, Franchini M, Di Minno G. Understanding inhibitor development in haemophilia A: towards clinical prediction and prevention strategies. Haemophilia. 2010;16(Suppl 1):13-19.
4. Gouw SC, van der Bom JG, Ljung R, et al. Factor VIII products and inhibitor development in severe hemophilia A. N Engl J Med. 2013;368:231-239.
5. Vezina C, Carcao M, Infante-Rivard C, et al. Incidence and risk factors for inhibitor development in previously untreated severe haemophilia A patients born between 2005 and 2010. Haemophilia. 2014;20:771-776.
6. Peyvandi F, Mannucci PM, Garagio I, et al. A randomized trial of factor VIII and neutralizing antibodies in hemophilia A. N Engl J Med. 2016;374:2054-2064.
7. Fischer K, Lassila R, Peyvandi F, et al. Inhibitor development in haemophilia according to concentrate. Four-year results from the European HAemophilia Safety Surveillance (EUHASS) project. Thromb Haemost. 2015;113:968-975.
8. Gouw SC, van der Bom JG, van den Berg HM. Treatment-related risk factors for inhibitor development in previously untreated patients with hemophilia A: the CANAL cohort study. Blood. 2007;109:4648-4654.
9. Marcucci M, Mancuso ME, Santagostino E, et al. Type and intensity of FVIII exposure on inhibitor development in PUPs with haemophilia A. A patient-level meta-analysis. Thromb Haemost. 2015;113:958-967.
10. Astermark J. Why do inhibitors develop? Principles of and factors influencing the risk for inhibitor development in haemophilia. Haemophilia. 2006;12(Suppl 3):52-60.
11. Carcao MD, van den Berg HM, Ljung R, Mancuso ME, PedNet and the Rodin Study Group. Correlation between phenotype and genotype in a large unselected cohort of children with severe hemophilia A. Blood. 2013;121:3946-3952.
12. Gouw SC, van der Bom JG, Auerswald G, Ettighausen CE, Tedgard U, van den Berg HM. Recombinant versus plasma-derived factor VIII products and the development of inhibitors in previously untreated patients with severe hemophilia A: the CANAL cohort study. Blood. 2007;109:4693-4697.
13. Oldenburg J. Optimal treatment strategies for hemophilia: achievement and limitations of current prophylactic regimens. Blood. 2015;125:2038-2044.
14. Gouw SC, van den Berg HM, Fischer K, et al. Intensity of factor VIII treatment and inhibitor development in children with severe hemophilia A: the RODIN study. Blood. 2013;121:4046-4055.
15. European Medicines Agency. Guideline on Immunogenicity Assessment of Biotechnology-derived Therapeutic Proteins. EMEA/CHMP/BMWP/14327/2006 Rev. 1; 2015. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2015/10/WC500194507.pdf. Accessed March 30, 2017.
16. Xi M, Makris M, Marcucci M, Santagostino E, Mannucci PM, Iorio A. Inhibitor development in previously treated hemophilia A patients: a systematic review, meta-analysis, and meta-regression. J Thromb Haemost. 2013;11:1655-1662.
17. Kannicht C, Ramstrom M, Kohla G, et al. Characterisation of the post-translational modifications of a novel, human cell line-derived recombinant human factor VIII. Thromb Res. 2013;131:78-88.

18. Sandberg H, Kannicht C, Stenlund P, et al. Functional characteristics of the novel, human-derived recombinant FVIII protein product, human-cl rhFVIII. Thromb Res. 2012;130:808-817.

19. Franchini M, Lippi G. Von Willebrand factor-containing factor VIII concentrates and inhibitors in haemophilia A. A critical literature review. Thromb Haemost. 2010;104:931-940.

20. Kreuz W, Escuriola Ettingshausen C, Vdovin V, et al. First prospective report on immune tolerance in poor risk haemophilia A inhibitor patients with a single factor VIII/von Willebrand factor concentrate in an observational immune tolerance induction study. Haemophilia. 2016;22:87-95.

21. European Medicines Agency. Assessing the Efficacy and Safety of Human Plasma Derived Factor VIII:C and Factor IX:C Products in Clinical Trials in Haemophiliacs Before and After Authorisation. (CPMP/BPWP/198/95); 1996. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2015/10/WC500194507.pdf. Accessed June 30, 2017.

22. Calvez T, Chambost H, Claeyssens-Donadel S, et al. Recombinant factor VIII products and inhibitor development in previously untreated boys with severe haemophilia A. Blood. 2014;124:3398-3408.

23. Kreuz W, Ettingshausen CE, Auerswald G, et al. Epidemiology of inhibitors and current treatment strategies. Haematologica. 2003;88:EREPO4.

24. Goudemand J, Rothschild C, Demiguel V, et al. Influence of the type of factor VIII concentrate on the incidence of factor VIII inhibitors in previously untreated patients with severe haemophilia A. Blood. 2006;107:46-51.

25. Mancuso ME, Mannucci PM, Rocino A, Garagiola I, Tagliacere A, Santagostino E. Source and purity of factor VIII products as risk factors for inhibitor development in patients with haemophilia A. J Thromb Haemost. 2012;10:781-790.

26. Wight J, Paisley S. The epidemiology of inhibitors in haemophilia A: a systematic review. Haemophilia. 2003;9:418-435.

27. Iorio A, Halimith Salz, Holzhauer S, et al. Rate of inhibitor development in previously untreated hemophilia A patients treated with plasma-derived or recombinant factor VIII concentrates: a systematic review. J Thromb Haemost. 2010;8:1256-1265.

28. Franchini M, Tagliacere A, Mengoli C, Cruciani M. Cumulative inhibitor incidence in previously untreated patients with severe hemophilia A treated with plasma-derived versus recombinant factor VIII concentrates: a critical systematic review. Crit Rev Oncol Hematol. 2012;81:82-93.

29. Franchini M, Coppola A, Rocino A, et al. Systematic review of the role of FVIII concentrates in inhibitor development in previously untreated patients with severe hemophilia A: a 2013 update. Semin Thromb Hemost. 2013;39:752-766.

30. Kurnik K, Bidlingmaier C, Engl W, Chehadeh H, Reipert B, Auerswald G. New early prophylaxis regimen that avoids immunological danger signals can reduce FVIII inhibitor development. Haemophilia. 2010;16:256-262.

31. Auerswald G, Kurnik K, Aledort LM, et al. The EPIC study: a lesson to learn. Haemophilia. 2015;21:622-628.

32. Delignat S, Dasgupta S, Andre S, et al. Comparison of the immunogenicity of different therapeutic preparations of human factor VIII in the murine model of hemophilia A. Haematologica. 2007;92:1423-1426.

33. Astermark J, Altsert C, Batorova A, et al. Non-genetic risk factors and the development of inhibitors in haemophilia: a comprehensive review and consensus report. Haemophilia. 2010;16:747-766.

34. Witmer C, Young G. Factor VIII inhibitors in hemophilia A: rationale and latest evidence. Ther Adv Hematol. 2013;4:59-72.

35. Schwaab R, Brackmann HH, Meyer C, et al. Haemophilia A: mutation type determines risk of inhibitor formation. Thromb Haemost. 1995;74:1402-1406.

36. Bjorkman S, Blanchette VS, Fischer K, et al. Comparative pharmacokinetics of plasma- and albumin-free recombinant factor VIII in children and adults: the influence of blood sampling schedule on observed age-related differences and implications for dose tailoring. J Thromb Haemost. 2010;8:730-736.

37. Blanchette VS, Shapiro AD, Liesner RJ, et al. Plasma and albumin-free recombinant factor VIII: pharmacokinetics, efficacy and safety in previously treated pediatric patients. J Thromb Haemost. 2008;6:1319-1326.

38. Morfini M, Marchesini E, Paladino E, Santoro C, Zanon E, Iorio A. Pharmacokinetics of plasma-derived vs. recombinant FVIII concentrates: a comparative study. Haemophilia. 2015;21:204-209.

39. Nowak-Gottlik S, Grumpel A, Russo A, Jansen M. Efficacy and safety of Wilate® in paediatric VWD patients under 6 years of age - results of a prospective multicentre clinical study including recovery information. Haemophilia. 2013;19:887-892.

40. Klukowska A, Szczepanski T, Vdovin V, Knaub S, Jansen M, Liesner R. Novel, human cell line-derived recombinant factor VIII (Human-cl rhFVIII, Nuwiq®) in children with severe haemophilia A: efficacy, safety and pharmacokinetics. Haemophilia. 2016;22:232-239.

How to cite this article: Klukowska A, Komrskova V, Vdovin V, et al. Low incidence of factor VIII inhibitors in previously untreated patients with severe haemophilia A treated with octanate®: Final report from a prospective study. Haemophilia. 2018;24:221-228. https://doi.org/10.1111/hae.13385