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REVIEW

Human plasma-derived FVIII/VWD concentrate (Biostate): a review of experimental and clinical pharmacokinetic, efficacy and safety data

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Abstract

Human plasma-derived factor VIII/von Willebrand factor complex concentrates are used to control bleeding in patients with von Willebrand disease (VWD) or haemophilia A (HA). The properties of these haemostatic factor concentrates vary widely, which can have significant clinical implications.

This review provides an extensive overview of the molecular properties, in addition to pharmacokinetic, efficacy and safety data, and case studies of clinical experience of one such concentrate, Biostate. These data are discussed in the context of various therapeutic applications and compared with other factor concentrate products. Data are presented from data on file from the manufacturer; product information and published experimental and clinical pharmacokinetic, safety and efficacy study data; and example case studies of clinical experience.

The data discussed herein demonstrate that Biostate has well-established efficacy profiles in the treatment of patients with VWD or HA, with the control of bleeding rated as 'excellent', 'good' or 'moderate' in >90% of patients. In an immune-tolerance induction setting, 73% of patients achieved a complete response following treatment with Biostate. Biostate was generally well tolerated in patients with HA or VWD, with infrequent minor adverse events reported and no reported cases of clinically relevant thrombosis.

Keywords: von Willebrand diseases, haemophilia A, von Willebrand factor, factor VIII, immune tolerance, haemorrhage, factor VIII/von Willebrand factor concentrate, treatment efficacy.

Abbreviations: AE, adverse event; AHF-HP, antihaemophilic factor-high purity; AUC, area under curve; B19V, human parvovirus B19; DDAVP, desmopressin (1-deamino-8-D-arginine); FVIII, factor VIII; HA, haemophilia A; HMWM, high-molecular-weight multimer; ITI, immune-tolerance induction; LRF, logarithmic reduction factor; NHP, normal human plasma; PK, pharmacokinetic; PrP^{sc}, experimentally spiked infectious prion protein; SD, solvent detergent; TE, thromboembolic event; VWD, von Willebrand disease; VWF, von Willebrand factor; VWF:Ag, von Willebrand factor antigen

Citation

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Introduction

Management of congenital bleeding disorders, such as von Willebrand disease (VWD) and haemophilia A (HA), is complex due to the variety of clinical symptoms, bleeding type and bleeding severity. Current strategies used to control bleeding in patients with VWD are as follows: (i) nonreplacement therapy with desmopressin (1-deamino-8-D-arginine [DDAVP]) to elevate endogenous von Willebrand factor (VWF) and factor VIII (FVIII) concentrations; (ii) replacement therapy using transfusion of human plasma-derived FVIII/VWF concentrates to elevate VWF plasma concentration; and (iii) other biological therapies, for example, topical agents for minor bleeding, hormonal treatment for women with menorrhagia and antifibrinolytics used alone or as adjunct therapy to treat bleeding in VWD [1,2].

DDAVP treatment results in the release of endogenous VWF [3,4]; therefore, its use in the treatment of patients with type 2 or type 3 VWD can be less efficacious than treatment with VWF concentrates [2]. In patients unresponsive to DDAVP or where the use of DDAVP is contraindicated, FVIII/VWF concentrate

Table 1. Key properties of various factor VIII/von Willebrand factor concentrates.

	Biostate [6–8]	Haemate P/Humate-P [9,10]	Alphanate [9,11]	Fanhdi [9,12]	Immunate [9,13]	Wilate [14,15]
HMWM VWF (% of NHP)	86[a] [6]	93.6 [9]	29.3 [9]	31.7 [9]	3.9 [9]	N/A
VWF:RCo/VWF:Ag	0.72–0.95 [7]	0.91 [9]	0.43 [9]	0.69 [9]	0.38 [9]	0.9–1.0 [14]
VWF:CB/VWF:Ag	0.73–0.99 [7]	0.89 [9]	0.49 [9]	0.47 [9]	0.21 [9]	N/A
VWF:RCo/FVIII:C	2.00 [8]	2.88 [9]	0.82 [9]	1.29 [9]	0.67 [9]	1.0 [14]
VWF:CB/FVIII:C	N/A	2.28 [9]	0.68 [9]	0.80 [9]	0.16 [9]	N/A
Specific VWF:RCo activity (IU/mg)	100[b] [8]	5–17[c] [10]	N/A	N/A	N/A	≥67[c] [15]
Specific FVIII:C activity (IU/mg)	70[b] [8]	2–6[c] [10]	>100[b] [11], >5[d] [11]	2.5–10[c] [12]	70 ± 30[c] [13]	≥67[c] [15]

FVIII:C, factor VIII coagulant activity; HMWM, high-molecular-weight multimers; N/A, not available; NHP, normal human plasma; VWF, von Willebrand factor; VWF:Ag, antigen; VWF:CB, collagen binding assay; VWF:RCo, ristocetin cofactor.
[a]HMWM content of Voncento; [b]Measured prior to the addition of albumin stabiliser; [c]No information provided regarding stabiliser; [d]Specific activity in Alphanate as a finished product.

is recommended [2]. FVIII/VWF concentrates serve to replace endogenous VWF in patients with VWD and several FVIII/VWF concentrates are commercially available for the treatment of patients with VWD.

FVIII concentrates, whether plasma-derived or recombinant, are the primary treatment option in patients with congenital HA and are provided either in a prophylactic manner or for on-demand treatment [5]. Other treatments such as DDAVP, fibrin glue or tranexamic acid may be used alone or as an adjunct to FVIII concentrate use in patients with mild HA [5].

Significant heterogeneity exists between FVIII/VWF concentrates (Table 1 [6–15]) and is a factor to consider when they are used in clinical practice [9]. Biostate* is the human plasma-derived FVIII/VWF concentrate currently used in Australia and New Zealand and has been available in these regions since 2003 and 2005, respectively. This review provides an overview of the development; product characteristics; experimental and clinical pharmacokinetic (PK), safety and efficacy data; and clinical experience of Biostate over the past 10 years. These data are discussed in the context of various therapeutic applications and compared with other factor concentrate products.

Methods

A combination of Biostate data is presented, reviewed and discussed. These data are from (i) data on file from the manufacturer; (ii) product information; (iii) published experimental studies; (iv) published clinical PK, safety and efficacy studies; and (v) case studies of authors' clinical experience. A PubMed search on Biostate, without limits, was also performed.

*Biostate is a registered trademark of CSL Behring Pty Ltd, Broadmeadows, Australia.

Results

History and rationale for the development of Biostate

Prior to the introduction of Biostate in Australia and New Zealand, the plasma-derived FVIII/VWF concentrate used to treat VWD and HA was antihaemophilic factor-high purity (AHF-HP) (manufactured in Australia by CSL from 1989). AHF-HP is now regarded as a product of intermediate purity (in relation to FVIII specific activity) compared with current international standards. AHF-HP had one dedicated virus-inactivation step (dry-heat treatment).

Biostate was registered in Australia in August 2000; AHF-HP was deregistered in Australia in 2003. Biostate was subsequently developed based on the production process of AHF-HP.

The Biostate manufacturing process includes purification of FVIII/VWF from cryoprecipitate using selective precipitation and size exclusion chromatography and two dedicated virus-inactivation steps [8]. These consist of an incubation period with a solvent/detergent (SD) suspension (tri-n-butyl phosphate and polysorbate 80), followed by lyophilisation/dry-heat treatment at 80°C for 72 hours [8]. The SD step inactivates enveloped viruses, including blood-borne viruses of major concern in plasma-derived products, such as human immunodeficiency viruses, hepatitis B virus and hepatitis C virus (Table 2) [8]. Additionally, the Biostate lyophilisation/dry-heat treatment process inactivates enveloped and nonenveloped viruses and contributes to the inactivation of human parvovirus B19 (Table 2) [8]. The Biostate manufacturing process has also been investigated for its potential to deplete experimentally spiked infectious prion protein (PrP^{sc}). The cumulative PrP^{sc} logarithmic reduction factors (LRFs) for

Table 2. Viral logarithmic reduction factors for various stages of the Biostate manufacturing process (CSL Behring, data on file).

Process stage	Biostate 50 IU/mL					Biostate 100 IU/mL					
	HIV	HAV	HBV	HCV	B19V	HIV	HAV	HBV	HCV	B19V	WNV
Cryoprecipitate collection	NT	≥4.1	NT	NT	NT	NT	≥4.1	NT	NT	NT	NT
Solvent detergent virus inactivation	≥5.2	NT	≥5.6	≥6.3	NT	≥5.2	NT	≥5.6	≥6.3	NT	NT
Lyophilisation/80°C for 72 hours	≥4.7	≥7.3	≥6.2	≥7.2	≥6.5	≥5.8	≥5.6	≥2.9	≥5.6	≥3.2	≥5.6
Total validated virus reduction	≥9.9	≥11.4	≥11.8	≥13.5	≥6.5	≥11.0	≥9.7	≥8.5	≥11.9	3.2	≥5.6

Validation of pathogen inactivation was achieved by experimentally spiking the plasma product with the pathogen of interest before the various process stages. Logarithmic reduction factor (LRF) equals viral load input minus viral load output; LRF values of ≥4 indicate a significant reduction of viral load during a particular production stage.
B19V, human parvovirus B19; HAV, hepatitis A virus; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; NT, not tested; WNV, West Nile virus.

experimentally introduced animal prions [16] were found to align with LRF values included in recommendations from the US Food and Drug Administration and the European Medicines Agency [17,18].

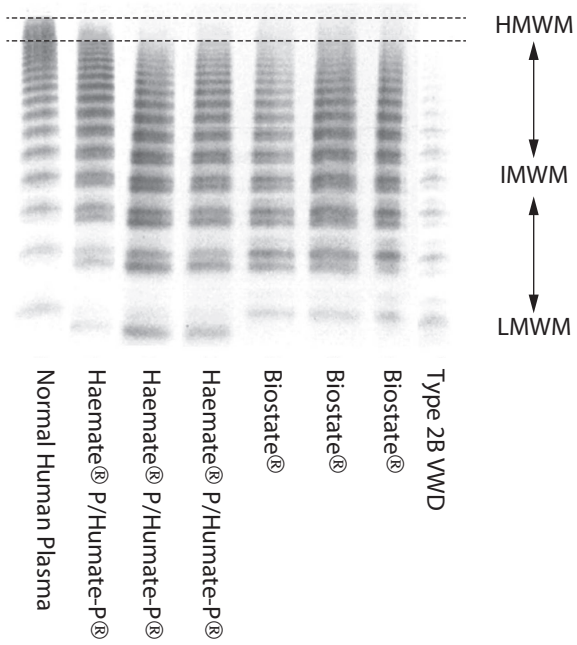
Properties of Biostate

VWF is the largest protein found in plasma, circulating as a series of multimers, which contain a variable number of subunits ranging in size between 500 and 20,000 kDa [19]. The high molecular weight multimers (HMWM) of VWF possess the haemostatic properties exhibited by VWF, with smaller multimers possessing VWF:RCo activity but lacking platelet aggregation characteristics [20–22]. *In vitro* analyses of commercially available FVIII/VWF concentrates highlighted wide variation in their properties, including their HMWM content and similarity to normal human plasma (NHP) [9,23]. The VWF multimeric profile of Biostate has been demonstrated to be similar to NHP and Haemate P/Humate-P (CSL Behring) (Figure 1) [7].

VWF functional activity

The 'specific' functional activity of VWF in FVIII/VWF concentrates can be assessed by determining ratios of VWF:RCo activity or VWF:CB activity against the total amount of VWF antigen (VWF:Ag) present. Furthermore, these ratios have been shown to correlate well with the HMWM VWF content of FVIII/VWF concentrates, a property which is indicative of VWF haemostatic potential [9]. The National Institute for Health guidelines for the diagnosis and evaluation of VWD define a VWF:RCo/VWF:Ag ratio of <0.5–0.7 as indicative of dysfunctional VWF [2]; therefore, it has been suggested that FVIII/VWF concentrates displaying VWF:RCo/VWF:Ag ratios >70% of NHP (or ratios above 0.7) are highly active [9]. When compared with AHP-HP and Haemate P/Humate-P, Biostate possesses a VWF:RCo/VWF:Ag ratio in the range of 0.72–0.95 and a VWF:CB/VWF:Ag ratio in the range of 0.73–0.99. These values suggest a highly functional activity of VWF in Biostate [7].

Figure 1. von Willebrand factor multimer profiles of Biostate compared with Haemate P/Humate-P and pooled normal human plasma (figure courtesy of EJ Favaloro).



Plasma from a patient with type 2B VWD was included to demonstrate characteristic loss of HMWM VWF associated with this type of VWD.
HMWM, high-molecular-weight multimers; IMWM, intermediate-molecular-weight multimers; LMWM, low-molecular-weight multimers; Type 2B VWD, type 2B von Willebrand disease; VWF, von Willebrand factor.

FVIII/VWF ratio

Elevated plasma FVIII concentrations have been associated with an increased risk of thromboembolic events (TEs); the Leiden thrombophilia study demonstrated that plasma FVIII concentrations of ≥150 IU/mL are associated with

Table 3. Pharmacokinetic data for von Willebrand factor following a single dose of Biostate in patients with von Willebrand disease [31, CSL Behring, data on file].

	Half-life (h)	Recovery (%)	Clearance (mL/h/kg)	$AUC_{0-\infty}$ (IU/mL×h)[a]
VWF:RCo	11.6 (7.6–15.6)	85 (77–92)	4.2 (3.0–5.5)	18.1 (6.1–49.7)
VWF:CB	12.2 (9.8–14.6)	82 (45–131)	4.9 (3.9–6.0)	12.4 (6.68–18.74)
VWF:Ag	13.9 (11.7–16.1)	70 (29–114)	2.8 (2.3–3.3)	20.4 (11.22–32.36)

Mean (90% CI).
[a]Values in brackets denote ranges.
AUC, area under curve; CI, confidence interval; VWF:Ag, von Willebrand factor antigen; VWF:CB, von Willebrand factor collagen binding activity; VWF:RCo, von Willebrand factor ristocetin cofactor activity.

an adjusted odds ratio of 4.8 for increased risk of venous thromboembolism [24,25]. Plasma FVIII can increase upon repeated dosing with FVIII/VWF concentrates owing to supplementation to already appreciable levels of endogenous FVIII; this is further exacerbated by stabilisation of both endogenous and exogenous FVIII by VWF [26]. The apparent plasma elimination half-life of FVIII:C can therefore be up to three times longer than that of VWF:RCo, leading to greater increases of FVIII:C than VWF in plasma [26,27]. Consequently, there have been reports of TEs following treatment of patients with VWD with FVIII/VWF concentrates; however, these were very rare, occurring when other risk factors for TEs were present [26–29]. Therefore, many authors recommend close monitoring of FVIII:C concentrations when using FVIII/VWF concentrates with high VWF to FVIII ratios, and thromboprophylaxis should be considered in patients at a high risk of thrombosis, particularly following surgery [23,26,28,30]. Biostate contains a high ratio of VWF to FVIII (approximately 2:1) and could be suitable for use in patients with VWD who require repeated doses of a FVIII/VWF concentrate [8].

Clinical data in patients with VWD or HA

The PK properties, safety and efficacy of Biostate in the treatment of patients with VWD or HA have been investigated in a number of prospective and retrospective studies. Furthermore, the effectiveness and tolerability of Biostate has also been demonstrated through post-marketing clinical experience gained to date, as exemplified through case studies presented below.

PK properties of Biostate in patients with VWD

The PK properties of Biostate in patients with VWD were measured during a multicentre trial comparing Biostate with AHF-HP (CSL Behring), in which 12 patients, aged 19–58 years, were recruited (5 type 1, 2 type 2B, 1 type 2M and 4 type 3 patients with VWD). These patients had VWF:RCo levels <20 IU/dL and/or VWF:Ag levels <30 IU/dL and were insufficiently responsive to DDAVP, or DDAVP was contraindicated. Patients were randomly assigned a single intravenous infusion of either Biostate or AHF-HP (60 IU/kg VWF:RCo; Infusion 1), followed by a 15-day washout period before administration of the alternate study concentrate (Infusion 2). Quantitative parameters for FVIII:C, VWF:RCo, VWF:CB and VWF:Ag, in addition to HMWM analysis and investigation of primary haemostasis parameters (evaluated using the PFA-100 assay [Siemens Healthcare]), were assessed at screening, before and 30 minutes after Infusions 1 and 2, and at the completion visit [31].

The PK properties following a single administration of Biostate are shown in Table 3 [31]. Area under curve (AUC) values for Biostate demonstrated similar PK properties to AHF-HP and other FVIII/VWF concentrates [31]. A high ratio of HMWM to low-MWM VWF was reported following infusion with Biostate and mirrored the observed high AUC ratios for VWF:RCo/VWF:Ag (0.85) and VWF:CB/VWF:Ag (0.61). These data indicate that the VWF within Biostate retains a high specific functionality post infusion, similar to that displayed in the native material (refer to section 'VWF functional activity' above).

Safety and efficacy of Biostate in patients with VWD

One company-sponsored prospective Phase II/III study and two retrospective multicentre studies have assessed the safety and efficacy of Biostate [32–34].

The prospective study recruited 23 patients, aged >3 years old (7 type 1, 9 type 2 and 7 type 3), who were insufficiently responsive to DDAVP or in whom the use of DDAVP was contraindicated. Efficacy assessments were performed on a total of 25 surgical events and 6 nonsurgical bleeds, in addition to prophylaxis treatment over 6–12 months in four patients [32]. Haemostatic outcomes in 100% of surgical patients were rated as excellent or good and 85% of surgery-treated events were considered to have less or equivalent blood loss compared with patients having no bleeding disorder. Additionally, all patients receiving Biostate prophylactically had excellent or good haemostatic outcomes based on the assessment of bleed frequency. With regard to nonsurgical bleeds, four of the six were rated to have excellent or good haemostatic efficacy, with all four of these events rated as having excellent outcomes. The remaining

two bleeds were a vaginal bleed (rated moderate efficacy) and recurrent gastrointestinal bleeding (efficacy rating: none for the first 3 days and good for the subsequent 5 days of treatment when the dose was increased from 14.5 to 26.1 IU/kg/day) [32]. Biostate was well tolerated during the course of treatment (median exposure was 8 days for all patients or 62 days in patients receiving Biostate for prophylaxis) with only three minor adverse events (AEs) reported as either possibly or probably due to treatment (minor elevation of liver function tests, moderate dyspnoea and injection site thrombophlebitis). Plasma FVIII:C and VWF:RCo levels remained within the target range for the majority of patients (≥89% of surgical events) over the course of the treatment, and there were no reported cases of deep vein thrombosis or pulmonary emboli [32].

Within the two retrospective studies that assessed the safety and efficacy of Biostate, one involved 43 patients with VWD aged 19–80 years (26 type 1, 12 type 2 and 5 type 3), undergoing 58 surgical procedures (24 major and 34 minor) across three Australian haemophilia treatment centres [34]. The second study focused on children and adolescents with VWD across eight haemophilia centres in Australia and New Zealand. Data were assessed for 43 patients with VWD aged 0.4–17 years (21 type 1, 4 type 2A, 6 type 2B, 4 type 2M, 1 type 2N and 7 type 3), undergoing a total of 42 surgical events (10 major and 32 minor) [33]. Both studies demonstrated that Biostate was efficacious and well tolerated in children and adolescents. Table 4 details the haemostatic efficacy results from these two studies [33,34]. It was noted that fewer 'excellent' responses were noted in patients with type 3 VWD compared with patients with type 1 or 2 VWD.

Clinical experience in patients with VWD: case study

A 6-year-old boy with type I VWD (baseline VWF:Ag 15 IU/dL and VWF:RCo 30 IU/dL) was hospitalised after presenting with marked iron deficiency anaemia (haemoglobin 5.2 g/dL and serum ferritin <2 ng/mL). Medical history included a DDAVP challenge at 5 years of age, for which the patient was deemed unresponsive, with an increase of VWF:Ag to 23 IU/dL and a VWF:RCo of 21 IU/dL at 4 hours post infusion. He had been referred to the ear, nose and throat (ENT) service 3 months earlier because of intermittent epistaxis and, at the time, underwent a chemical cauterisation of large nonbleeding vessels in the nasal mucosa. Two days after the procedure, he began to experience regular, short-lived epistaxis. The patient had been experiencing regular epistaxis (approximately three times per week lasting up to 15 minutes via both nares) 6 weeks prior to presentation, for which he had been treated with tranexamic acid with only limited effect. No history of other sources of blood loss was documented and he had what was considered a normal diet with iron-containing foods multiple times per week.

At presentation, the patient was pale but his cardiovascular system was stable. He did not have epistaxis at the time of presentation, with the bleeding having stopped on arrival to hospital, but examination revealed large nasal mucosal vessels. Considering the degree of anaemia and risk of further epistaxis, he was infused with Biostate 30 IU/kg, in addition to receiving tranexamic acid treatment (25 mg/kg three times per day), and was seen by the ENT service in the emergency department. The nasal mucosal vessels were chemically cauterised bilaterally and he was discharged with ongoing tranexamic acid and oral iron supplementation. Due to the severity of the anaemia, he received a further dose of Biostate 30 IU/kg 2 days

Table 4. Efficacy of Biostate in adults, adolescents and children with von Willebrand disease [33,34].

	Efficacy of Biostate in adult patients with VWD [33]			Efficacy of Biostate in young and adolescent patients with VWD [34]		
	No. of events	Excellent haemostasis (%)	Good haemostasis (%)	No. of events	Excellent haemostasis (%)	Good haemostasis (%)
VWD type						
1	32	81	19	26	73	12
2A	13	75	25	4	100	nil
2B	4	100	nil	12	67	33
2M				7	86	14
2N				1	nil	100
3	9	55	45	64	78	14
Surgical procedure						
Major	22	75	25	10	80	10
Minor	23	82	18	32	78	13

Excellent haemostasis: normal haemostasis, with blood loss equivalent to patient without a bleeding disorder; Good haemostasis: partial but adequate control of the bleeding, not requiring additional product or unplanned treatment. VWD, von Willebrand disease.

Table 5. Initial and repeat pharmacokinetic properties of Biostate in patients with haemophilia A (CSL Behring, data on file).

	Half-life (h)	*In vivo* recovery (%)	Clearance (mL/h/kg)	$AUC_{0-\infty}$ (IU/mL×h)
Initial study (n=16)	12.4 (11.1–13.7)	108 (91–124)	3.3 (2.9–3.6)	15.9 (14.5–17.3)
Repeat study (n=8)	14.14 (12.8–15.5)	110 (93–127)	3.0 (2.7–3.3)	14.8 (12.6–16.9)

Mean (95% CI). Pharmacokinetic evaluations were assessed using blood samples on Day 1 preinfusion, and at 10, 30 and 60 minutes and 3, 6, 9, 12, 24, 30, 36 and 48 (optional) hours post infusion.
AUC, area under curve; CI, confidence interval.

after his initial presentation. One week later, the patient was reviewed in clinic and his repeat haemoglobin was 7.1 g/dL with brisk reticulocytosis. The patient did not experience any further epistaxis.

PK data in patients with HA

The PK properties of Biostate following an initial dose (50 IU/kg) and a repeat dose 3–6 months later were determined in an open, multicentre study conducted in four Australian hospitals (CSL Behring, data on file). During this study, 16 patients were initially recruited (aged 17–53 years) and eight of these patients were included in the repeat assessment. The PK properties of Biostate in patients with HA were similar for the initial and repeat doses, though the half-life determined from the repeat study was noted to be longer (12.4 versus 14.14 hours for the initial and repeat studies, respectively); however, this difference was not statistically significant (Table 5).

Safety and efficacy data in patients with HA

The safety and efficacy of Biostate in patients with HA was assessed in an open, multicentre study in six hospitals in Australia and New Zealand. The study recruited 30 patients, aged 16–62 years, who had received plasma-derived FVIII replacement therapy for moderate to severe haemophilia. A total of 1,019 infusions of Biostate were administered for trauma, spontaneous bleeds or prophylaxis. In the 782 treated events included in the efficacy analysis, 78.6% of responses were rated by patients as excellent (15.8%) or good (62.8%); 17.4% of responses were rated as moderate. Safety analysis demonstrated Biostate was well tolerated in patients with HA, with only 13% of administrations resulting in AEs considered treatment-related by the investigator (four patients with 21 events), including headache (0.8% of infusions) and back pain (0.3% of infusions). Furthermore, no patients developed inhibitors to FVIII (CSL Behring, data on file).

Clinical experience in patients with HA: case study

A boy with severe HA (FVIII <1%) was diagnosed at birth. Other family members with HA had developed high-titre inhibitors that were difficult to eradicate, following treatment with recombinant FVIII. After discussion with the family, it was decided that, in an attempt to minimise inhibitor risk, he would be treated with Biostate rather than recombinant FVIII. Furthermore, treatment was avoided at times of immunisation and, where possible, peak exposure periods were avoided.

At 3 months of age, the patient developed an extensive epidural haematoma and was treated with 8-hourly bolus doses of Biostate for 1 week, followed by a week of twice-daily dosing, before starting prophylactic therapy every second day. One week post discharge, the 48-hour trough FVIII levels were 1% and a low-titre inhibitor was detected (0.8 Bethesda Units [BU]/mL), which persisted for a month despite dosing being increased from 35 to 70 IU/kg/dose every second day. The dosing was therefore increased to 70 IU/kg/day, following which, inhibitor levels became undetectable. Daily dosing of Biostate was continued for 12 months before his PK normalised and the dosing regimen was altered to second daily prophylaxis dosing of 35 IU/kg. The patient has had no breakthrough bleeds since commencing Biostate therapy. He remains well on prophylactic therapy every second day without recurrence of his inhibitor.

Immune-tolerance induction (ITI)

One of the main barriers to successful therapy with FVIII concentrates is the development of FVIII-neutralising alloantibodies, which dramatically reduce the haemostatic effect of these concentrates. ITI is a method of immune modulation in which frequent infusions and higher FVIII units are given to patients over months or years to eradicate inhibiting antibodies. It has been suggested that VWF-containing FVIII concentrates may increase the probability of ITI success, even when used as salvage therapy following unsuccessful ITI with other FVIII products [35]. The exact role of VWF in ITI is unknown; although, it is believed that VWF binding to FVIII protects FVIII from endocytosis by dendritic cells and subsequent presentation of FVIII peptides to immune effector T cells, which may reduce FVIII-specific immunogenicity [36,37]. However, it is important to note that Van Velzen et al. (2014) showed no difference in success rate for first-cycle ITI without immunomodulant comedication between VWF-containing FVIII concentrates and FVIII concentrates devoid of VWF [38].

Safety and efficacy of Biostate for ITI

The use of Biostate in ITI was assessed during a retrospective, observational cohort analysis at three Australian haemophilia treatment centres. The ITI of 15 paediatric patients

(aged 1.1–15.4 years) with severe HA were included in the analysis and comprised 8 patients who received Biostate for primary ITI and 7 patients who underwent salvage ITI. A wide variety of ITI regimens were observed, with the most common approach being a once-daily dose of 100 IU FVIII/kg (10 patients) [39].

At the end of the observation period, 11 patients (73.3%) had achieved a complete response (defined as an inhibitor titre of <0.6 BU/mL, with a normal FVIII recovery [>66% of predicted] and/or a normal FVIII half-life [>6 hours]) after a median duration of 21 months (range: 5–85 months). A further two patients (13.3%) achieved a partial response (inhibitor titre of <0.5 BU/mL with evidence of decreased FVIII:C survival but clinically relevant response to FVIII); therefore, the overall response rate was 86.6% [39]. Of the patients who received primary ITI, the overall response was 87.5% at 33 months; low-risk patients in this group had a complete response rate of 100%, whilst the overall response was 75% in those with poor prognostic factor indicators (i.e. historical peak inhibitor level >200 BU/mL, inhibitor level >10 BU/mL at the start of ITI, age >5 years, or >24 months between inhibitor detection and start of ITI) [39].

Clinical experience of Biostate in ITI: case studies

Case study 1: first-line ITI

A 65-year-old male with severe HA (FVIII <1%) developed a high-titre inhibitor (45 BU/mL) after a chronic soft tissue infection and exposure to high-intensity recombinant FVIII therapy received for surgical prophylaxis. Immunotolerance was initially induced with Biostate at a dose of 100 IU/kg/day until the inhibitor was eradicated. Subsequently, the dose was tapered to 50 IU/kg three times weekly, followed by a prophylactic dose of Biostate. He continued with a negative inhibitor titre on prophylactic bypass therapy until the time of his death 2 years later from hepatic malignancy.

Case study 2: salvage ITI

A 60-year-old male with mild HA developed an inhibitor after being exposed to high-intensity recombinant FVIII therapy as a 7-day continuous infusion for gallbladder surgery. He responded to his initial treatment of rituximab alone but relapsed after 17 weeks. He was retreated with rituximab, but this second remission was also not sustained. Once again, he was retreated with rituximab but, on this occasion, was also given Biostate 50 IU/kg three times weekly as ITI. This continued for a 12-month period in an attempt to maintain remission. This was successful; his FVIII level remained normal and his inhibitor was eradicated. He has been in remission for over 5 years and re-exposed to Biostate for minor surgical procedures.

Discussion

The efficacy and safety of Biostate has been demonstrated in patients with VWD or HA. In patients with VWD, haemostatic efficacy ratings for surgical procedures and nonsurgical bleeds in a broad age range (from 0.4 to 80 years) were 'excellent' or 'good' in >90% of patients [32–34]. These efficacy ratings are similar to those reported for other plasma-derived VWF/FVIII products, including Haemate P/Humate-P [40]. Biostate has been successfully used for prophylactic therapy in four patients with VWD and all patients' outcomes were rated as 'excellent' or 'good' in a Phase II/III prospective, multicentre study. The use of Biostate in patients with HA for successful on-demand and prophylactic therapy has been shown in an open, multicentre trial, with haemostatic efficacy ratings as 'excellent', 'good' or 'moderate' in 96% of patients and treatment being well tolerated (CSL Behring, data on file). A major concern in the treatment of patients with HA is the development of inhibitors, which occurs in approximately 21–52% of patients with severe HA, with most inhibitors developing in previously untreated patients within the first few exposure days (9–36 median exposure days) [41,42]. In the clinical trial described above, none of the 30 patients receiving Biostate for on-demand or prophylactic treatment developed FVIII-inhibitors over the 26-week observational period, though it should be noted that these patients had received FVIII-replacement therapy previously (CSL Behring, data on file).

In the case study described previously, the 2-year-old boy with a family history of high-titre inhibitor development did develop a low-titre inhibitor following treatment with Biostate; however, this was eradicated by increasing the dose, and the inhibitor has not recurred.

Patients with inhibitors require ITI, which is generally performed using recombinant FVIII products. ITI with Biostate resulted in 73% of patients achieving a complete response in a multicentre, retrospective study of patients with severe HA and inhibitors [39]. These response rates are equivalent to those observed with other plasma-derived concentrates (68% complete and partial success rate) and recombinant FVIII products (69% success rate), which are used in an off-label setting for ITI; however, it should be noted that differences in study design means these rates are not truly comparable [43,44]. Biostate has also been used in an off-label setting for ITI in patients with high-titre inhibitors, as exemplified here in the case studies of the 60 and 65-year-old patients with HA. One of these patients was successfully treated for salvage ITI after ITI with rituximab had failed.

Biostate has demonstrated good safety profiles in patients with VWD or HA, including during ITI, with only minor treatment-related AEs being reported and no reports of clinically relevant TEs [32–34,39].

Conclusion

Biostate is a high-purity FVIII/VWF concentrate available in Australia and New Zealand since 2003 and 2005, respectively. The manufacturing process of Biostate includes chromatographic fractionation and two dedicated and

complementary virus-inactivation steps, which have been validated to successfully demonstrate the removal of clinically relevant blood-borne viruses. Investigative studies have demonstrated the efficacy of the manufacturing process to remove experimentally spiked prions should they be present in the manufacturing pool. Biostate has a number of key properties, including retention of HMWM, demonstrating a VWF multimer profile similar to NHP; high VWF functional activity; and a high VWF:RCo/FVIII:C ratio. Furthermore, Biostate has an established safety and efficacy profile in patients with HA or VWD in both clinical trials and real-life settings.

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