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SHORT REPORT

Bleeding management in type 3 von Willebrand disease with anti-von Willebrand factor inhibitor: A literature review and case report

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Abstract

Treatment of type 3 von Willebrand disease by infusion of von Willebrand factor (VWF) and factor VIII (FVIII) concentrates may lead to the development of anti-VWF antibodies, challenging haemostasis management. The systematic review of the literature presented here retrieved 15 such cases (surgery $n = 11$, bleeding $n = 4$). The heterogeneous patient management mostly involved continuous infusion of FVIII, or recombinant FVIIa together with various other strategies. Off-label infusion of the bispecific monoclonal antibody emicizumab was prescribed in three cases and in a complex local case, ultimately well-controlled with emicizumab. This illustrates the fact that emicizumab appears as a therapeutic option in this context of allo-immunisation.

KEYWORDS
allo-antibodies, bleeding disorders, emicizumab, haemostasis, von Willebrand disease

1 | INTRODUCTION

Type 3 von Willebrand disease (VWD), an inherited blood disorder, is caused by a total deficiency of von Willebrand factor (VWF), associated to very low levels of factor VIII (FVIII) [1]. Bleeding manifestations are typically mucocutaneous (menorrhagia, epistaxis, gastrointestinal bleeding) or haematomas and haemarthrosis due to the absence of FVIII [2]. Surgery in such patients requires careful prophylaxis and surveillance.

Standard management of type 3 VWD involves prophylactic factor replacement with VWF concentrates or a combination of plasma-derived VWF-FVIII concentrates [3]. This leads to the development of allo-antibodies in 5%–10% of the cases [4], a rare condition with scarce management recommendations. Anti-VWF antibodies (commonly polyclonal IgG, mostly IgG4) do not inhibit FVIII activity [5], but lead to inefficient VWF replacement therapy. Moreover, they may induce life-threatening anaphylactic reactions [4]. Bleeding control in such patients is therefore challenging, as reaching normal VWF levels is important to prevent mucosal bleeds while normal FVIII levels are the main determinant of surgical haemostasis for joints and soft tissue interventions [6–8]. In the absence of VWF, the half-life of plasma FVIII is less than 2 h [5], and bleeding episodes would require the use of continuous FVIII intravenous infusion or boluses of recombinant activated factor VII (rFVIIa) [9].

To confirm the scarcity of information about such treatments, an up-to-date systematic review of the literature on the bleeding management for type 3 VWD patients with allo-antibodies was performed, and is presented and discussed here. The long history and management

of a local patient with allo-immunised type 3 VWD is also described, highlighting the efficacy of the more recent therapy emicizumab.

2 | MATERIALS AND METHODS

A PubMed search from 1981 until January 2024 was conducted to collect case reports or series, with the key words 'von Willebrand disease', 'von Willebrand disease, type 3', 'allo-antibodies', 'antibodies', 'neutralising antibodies', 'isoantibodies', 'low inhibitor' and 'treatment outcome', as well as Boolean combinations thereof (Supporting Information Appendix). Full-text articles published in English and describing patients, including children and adults diagnosed with type 3 VWD who developed allo-antibodies, with a detailed therapeutic strategy to manage haemostasis, including the type of replacement and/or non-replacement therapy and patient clinical course, were retained. From the 560 publications identified (Figure S1), 13 ultimately fulfilled inclusion criteria. An additional publication, not referenced in PubMed, was added based on the reference list of a review [10] consulted for setting the context.

3 | RESULTS

Published cases are detailed in Table 1, partitioned as surgery ($n = 11$) and bleeding ($n = 4$) management.

Surgery patients were seven women and four men, with a median age of 29 years (interquartile range [IQR]: 10–30). VWF inhibitors were reported in eight of these patients, with titres ranging from 0.7 to 166.5 Bethesda Units (BU)/mL. Four surgery reports were related to caesarean deliveries, the other seven being of various interventions. Highly heterogeneous schedules were used. At surgery time, the haemostatic strategy used recombinant FVIII (rFVIII) or FVIII/VWF concentrates in six cases, followed by rFVIIa ($n = 4$) and FXIII ($n = 1$) as single agents or in various combinations. Beside coagulation factors, tranexamic acid ($n = 3$), platelet transfusions, fibrinogen, fibrin glue, aprotinin, corticosteroids and anti-histamines were used as needed. Following surgery, management was also heterogeneous in relation to observed complications. This time, rFVIIa was the most used factor ($n = 7$), followed by various forms of FVIII. There were more platelet and red blood cell (RBC) transfusions, and tranexamic acid was used for three patients. Other prescriptions were of VWF, fresh plasma or corticosteroids. One thromboembolism was reported, consisting of an ilio-femoral thrombosis 19 days after initiation of rFVIIa, leading to placement of a cava filter. Of note, emicizumab was initiated post surgery in one patient (#10).

Four reports described the management of severe cutaneous-mucosal bleedings such as recurrent epistaxis, genitourinary or oropharyngeal bleedings, and recurrent haemarthrosis of the left ankle in two adults and two children, three of them having anti-VWF antibodies. Prophylactic haemostasis (Table 1) involved rFVIIa ($n = 2$), rFVIII ($n = 1$) or both alternating with prothrombin concentrate ($n = 1$, #15). Tranexamic acid was used in one patient (#12). Therapeutic adjustment involved various schedules of the same factors, with the addition of RBC transfusions, intravenous immunoglobulins, steroids or activated prothrombin complex concentrates. Of note, emicizumab was initiated in two patients (#14, #15) resulting in the disappearance of joint bleeds.

Increases in inhibitor titres were reported in two surgery and three bleeding cases.

This literature search had been prompted by the observation of a local case whose complete history is reported in Supporting Information. Briefly, this patient was diagnosed as a 3-year-old female with type 3 VWD, characterised by complete homozygous deletion within the VWF gene. Initially treated with occasional VWF concentrates, she developed allo-antibodies at age 8, which displayed fluctuating levels and increased post-partum when she was 24 years old. Upon an episode of subdural haematoma, she started to receive rFVIII for subsequent bleedings. Haemarthrosis developed that required surgery at age 41, essentially monitored by rFVIII, then suffered poorly controlled gastrointestinal bleedings. Upon initiation of emicizumab in 2019 (at age 47), now after 5 years, she only presented one bleeding episode and the VWF inhibitor has no longer been detected.

4 | DISCUSSION

Because of the rarity of both type 3 VWD and allo-immunisation to VWD, very few cases have been reported about haemostasis management in this setting. The literature search reported here highlights the heterogeneity of prophylactic and therapeutic strategies in this context, both in case of surgery and for spontaneous bleeds. Overall, initial treatment with rFVIIa alone required therapeutic escalation in half the cases. The addition of rFVIIa was less frequently needed when FVIII or FVIII/VWF alone were initially used. The FVIII + rFVIIa combination was rarely proposed. Analysis of these reports indicates that continuous injection of FVIII concentrates appears to be an appropriate first-line treatment option, as recommended by experts [5, 9], while the use of rFVIIa alone seems to be a viable strategy [11] in the case of low-risk surgery or minor bleeding. For mucosal haemorrhages, several haemostatic therapies may need to be combined to achieve sufficiently sustained haemostasis.

Bone surgery is at high risk of bleeding, and it is necessary to maintain high levels of FVIII:C until complete healing. In the local case reported here, continuous infusion of rFVIII alone with only FVIII:C monitoring was sufficient for surgical haemostasis and no by-passing agent was used. An increase of the inhibitor was detected after the onset of continuous infusion, a phenomenon also observed by Franchini et al. [10]. This transient increase could be explained by the presence of traces of VWF in washed RBC units that can contain residual platelets, despite RBC being deplasmatised and washed. Octocog alfa, derived from a baby hamster kidney cell-line (Helixate, Kogenate), can be used because this cell-line does not express recombinant human VWF [12]. Contrarily, octocog alfa derived from a Chinese hamster ovary cell line (Recombinate, Advate) could contain traces of VWF, as it co-expresses both VWF and rFVIII [13]. Although purification steps allow to separate

TABLE 1 Haemostatic strategy and clinical outcome of patients with allo-immunised type 3 von Willebrand disease.

	References[a]	Patient#	Age/ gender	Surgery/bleeding events	VWF inhibitors (BU/mL)	Haemostatic strategy	Clinical response and therapeutic adjustment	Inhibitor increase	Thrombo-embolic event
Surgery management	Ciavarella et al., 1996 (S1)	1,2	15/M (Patient 1) 23/M (Patient 2)	Multiple dental extractions in two brothers	Patient 1: 3 Patient 2: 48	Bolus of 150 µg/kg rFVIIa before and 2 h after surgery + IV tranexamic acid orally for 10 days + fibrin glue + rFVIIa 90 µg/kg every 2 h for 24 h, then every 3 h for an additional 24 h	Patient 1 suffered from prolonged bleeding, treated by 200 µg/kg rFVIIa every 2 h for 36 h	NS	No
	Boyer-Neumann et al., 2003 (S2)	3	29/F	Caesarean	16	CI rFVIII 35 IU/kg/h	Haemorrhagic return of menses, treated by 80 µg/kg of rFVIIa every 4 h + embolisation of uterine arteries	NS	Yes
	Dietrich et al., 2005 (S3)	4	29/M	Wound debridement and sutures	17	Urgent surgery without haemostatic prophylaxis	Post-operative bleeding treated by successive injections over 2 days of aprotinin 100 KIU/h for 24 h, FVIII 4000 IU twice, rFVIIa 100 µg/kg twice, FVIII 2000 IU, FXIII 2500 IU, fibrinogen 1 g and rFVIIa 180 µg/kg. The patient received a total of 8 RBCU	NS	No
	Pergantou et al., 2012 (S4)	5	9/M	Bone tumour removal	0.7	Bolus of rFVIII 60 IU/kg + IV rFVIIa 90 µg/kg CI rFVIII 25 IU/kg/h + rFVIIa every 2–3 h for 2 weeks	Recurrent haemarthrosis during physiotherapy, treated by CI rFVIII + rFVIIa 120 µg/kg once a day during physiotherapy	NS	No
	Martín-Salces et al., 2012 (S5)	6	30/F	Caesarean	1.5	Bolus of 100 IU/kg FVIII/VWF concentrates + CI FVIII/VWF 10 IU/kg/h Steroids and anti-histamines used as premedication to avoid anaphylactic reaction	Mild uterine bleeding 2 h after surgery treated by 2 RBCU + platelet infusions + tranexamic acid Intramural uterine haematoma at Day 3 treated by a bolus of 60 IU/kg and increase of CI from 3 to 8 IU/kg/h of FVIII/VWF concentrate Chills and arthralgia during treatment managed by antihistaminic drugs and steroids administered every 8 h	NS	No

(Continues)

TABLE 1 (Continued)

References[a]	Patient#	Age/ gender	Surgery/bleeding events	VWF inhibitors (BU/mL)	Haemostatic strategy	Clinical response and therapeutic adjustment	Inhibitor increase	Thrombo-embolic event
Scott, et al., 2018 (S6)	7	29/F	Caesarean	NS	Bolus of 270 µg/kg rFVIIa + platelet infusion once in established labour Delivery: rFVIIa, tranexamic acid and platelet infusions every 2 h	Uterine atony (1800 mL blood loss) treated by intrauterine misoprostol + IV oxytocin + balloon tamponade	Yes	No
Nummi et al., 2019 (S7)	8	49/F	Colonoscopy for gastrointestinal bleeding	NS	FVIII/VWF concentrate 40 IU/kg before + FVIII/VWF concentrate 20 IU/kg twice daily	FVIII/VWF concentrate + tranexamic acid every 6 h + pdFVIII every 4 h + platelet infusions + fresh frozen plasma + RBCU + IVIG 1 g/kg every 24 h 4 times	Yes	No
Faganel Kotnik et al., 2019 (S8)	9	6/F	Removal of a cyst of the branchial cleft remnants	Unknown	Pd VWF/FVIII 60 IU/kg + tranexamic acid before + pd VWF/FVIII 20 IU/kg + tranexamic acid every 8 h + pd VWF/FVIII 60 IU/kg at Day 2	Inhibitor status unknown before surgery, blood oozing from surgical site at Day 2 rFVIIa 90 µg/kg every 3 h + tranexamic acid + CI rFVIII 20 IU/kg/h after one 80 IU/kg bolus + 1 RBCU	NS	No
Shanmukhaiah et al., 2021 (S9)	10	6/F	Curettage of a mandibular pseudotumour	166.5	rFVIIa 90 µg/kg	Post-operative bleeding treated by rFVIIa 90 µg/kg every 3 h and FVIII continuous infusion 25 IU/kg/h, then rFVIIa same dose every 4 h and rFVIII 100 IU/kg/h daily. From Day 5 on, the patient received rFVIII 75 IU/kg twice a day until Day 14, together with one dose of rituximab 375 mg/m^2 at Day 4 Emicizumab initiated at Day 6	NS	No
Chikasawa et al., 2022 (S10)	11	30/F	Caesarean	1.1	CI rFVIII 30 IU/kg/h + boluses of pd VWF/FVIII 70 IU/kg + hydrocortisone Pd VWF/FVIII 35 IU/kg/day in VWF from Day 2 to Day 6	Blood loss during caesarean section (1695 mL including amniotic fluid)	NS	No

(Continues)

TABLE 1 (Continued)

	References[a]	Patient#	Age/ gender	Surgery/bleeding events	VWF inhibitors (BU/mL)	Haemostatic strategy	Clinical response and therapeutic adjustment	Inhibitor increase	Thrombo-embolic event
Bleeding management	Grossman et al., 2000 (S11)	12	51/M	Recurrent epistaxis	Present	rFVIIa 90 µg/kg 1–2/bleed + per os tranexamic acid (4 × 500 mg)	Poor response at the fourth episode after 14 injections of rFVIIa, tranexamic acid, local tamponade and electrocoagulation. Epistaxis resolved with injections of pd FVIII/VWF pd FVIII/VWF concentrates used for further epistaxis led to anaphylactic reaction Muscle haematoma of the left thigh was treated with boluses and CI of rFVIIa and tranexamic acid	Yes	No
	Franchini et al., 2008 (S12)	13	35/F	Macroscopic haematuria, haemorrhagic ovarian follicular rupture, menorrhagia, arm haematoma	NS	Bolus of 5000 IU of rFVIII + CI 1500 IU/h of rFVIII	Skin rash after a rFVIII bolus, no recurrence after steroid premedication	Yes	No
	Weyand et al., 2019 (S13)	14	5/M	Left ankle repeated haemarthrosis	Present	rFVIIa 270 µg/kg × 3/week Emicizumb 3 mg/kg/week for 4 weeks, followed by 1.5 mg/kg/ week	Recurrence of haemarthroses within left target ankle APCC prophylaxis plus rFVIIa for breakthrough bleeding Persistent rare spontaneous haemarthroses and significant treatment burden No further joint bleed	NS	No
	Cefalo et al., 2020 (S14)	15	2/M	Mucocutaneous bleeds	116	rFVIII or rFVIIa or prothrombin complex concentrate Emicizumab 3 mg/kg/week for 4 weeks, followed by 1.5 mg/kg/ week	Repeated and severe life-threatening mucocutaneous haemorrhages with need of several RBCU transfusions, IVIG, pdVWF and FVIII concentrate (bolus and CI) Rare and mild mucocutaneous bleedings without any hospitalisation or RBC transfusion No new spontaneous joint bleeding	No	No

Abbreviations: aPCC, activated prothrombin complex concentrate; CI, continuous infusion; F, female; FVIII, factor VIII; FXIII, factor XIII; IG, immunoglobulin; IV, intravenous; M, male; NS, not specified; pd, plasma derived; RBCU, red blood cell unit; rFVIIa, recombinant factor VII activated; rFVIII, recombinant factor VIII; VWF, von Willebrand factor.

[a]Chronological order per section.

the two products, some traces of VWF may remain, which could induce an anamnestic response.

Off-label use of emicizumab has been reported as a prophylactic treatment in eight patients with type 3 VWD, three of them being allo-immunised [13], and has been used here in three from the literature review and in the local case presented due to recurrent gastrointestinal bleeding. A body of evidence suggests that VWF is involved in angiogenesis, exposing patients with VWD to angiodysplasia, particularly in the digestive tract [14]. However, the very low levels of factor VIII and therefore significant reduction in thrombin generation in type 3 VWD probably contribute to the severity of digestive bleeding. Treatment by emicizumab was efficient and well tolerated, indicating that bleeding in type 3 VWD is largely the result of both FVIII and VWF/FVIII complexes deficiencies. Restoring part of the coagulation, the occurrence of spontaneous bleeding in daily life would thus be greatly reduced.

Although this treatment alone could be insufficient to provide the haemostasis necessary during major surgical procedures that demand high residual coagulation factor levels for a long period. A question is raised about minor surgeries usually treated with a few injections of clotting factor, which require lower levels of coagulation after the procedure. In these specific cases, emicizumab could be of great benefit to reduce the post-operative treatment burden. Finally, management of the rehabilitation phase could also be tricky, as described by Pergantou et al. in 2012 [15]. Sufficient haemostasis is needed to avoid haemorrhagic recurrence and delayed healing. rFVIII infusion before physiotherapy can be efficient, as in the case presented here, but emicizumab could also be an alternative. Good efficacy of emicizumab in this setting would again allow to reduce the treatment burden.

5 | CONCLUSION

The rare occurrence of both type 3 VWD and of allo-immunisation in this context makes conducting randomised studies with a large cohort of patients impossible. The surgical haemostatic management of such patients with continuous infusions of rFVIII appears to be a safe and effective therapeutic option. Mucocutaneous bleeding monitoring seems more complex to manage, often requiring a combination of therapies. Reporting clinical experience in this context is therefore important to improve and harmonise clinical practice. Finally, the use of emicizumab, successfully reported here in four patients with type 3 VWD and allo-antibodies, should be considered as a therapeutic option.

AUTHOR CONTRIBUTIONS

Aurélie Briane and Antoine Babuty performed the research. Aurélie Briane, Marianne Sigaud, Marc Trossaërt, Valérie Horvais, Nicolas Drillaud, Catherine Ternisien, Marc Fouassier and Antoine Babuty wrote the paper.

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CONFLICT OF INTEREST STATEMENT

Aurélie Briane and Marianne Sigaud declare they have no conflicts of interest. Marc Trossaërt has received research funding from NovoNordisk, Octapharma and Takeda, and acted as a paid consultant and received honoraria for participation in advisory boards for NovoNordisk, Roche, Sobi and Takeda. Valérie Horvais has received honoraria as speaker from Sobi. Nicolas Drillaud has received research funding from NovoNordisk, honoraria for participation in advisory boards for Roche and Octapharma and as speaker for Sobi. Catherine Ternisien has acted as a paid consultant and received honoraria for participation in advisory boards for LFB, Roche-Chugaï and Takeda. Marc Fouassier has received research funding from Sobi, NovoNordisk and Takeda, has acted as a paid consultant and received honoraria for participation in advisory boards for Sobi, Takeda, CSL Behring and Roche-Chugaï. Antoine Babuty has received research funding from Takeda and Bayer and acted as a paid consultant for Sobi.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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