Successful urgent neurosugery management with rFVIIa mega doses in a child with haemophilia A and high titre inhibitor

Laura Banov[a], Marco Pavanello[b], Gianluca Piattelli[b], Nicola Disma[d], Mariasavina Severino[c], Carlo Dufour[e] and Angelo Claudio Molinari[a]

We report an urgent aggressive neurosurgery procedure for a large life-threatening intracranial bleed in a 3-year-old boy with severe haemophilia A and high titre inhibitor, managed with mega doses of recombinant-activated FVII (rFVIIa). We infused preoperatively bolus of 350 μg/kg, repeated every 2 h for 4 days. There were no bleeding complications during surgery. Afterward, rFVIIa was gradually tapered acting alternatively on dose and timing, until the ongoing schedule of 214 μg/kg every 12 h.

To our knowledge this is the first report of aggressive neurosurgery in a boy with high titre inhibitor, successfully managed with high doses rFVIIa.

The close and prompt collaboration between haematologist, neurosurgeon, and anaesthesiologist was successful in managing the critical haemorrhage without major sequelae and eradicating the inhibitor, at a cost of about 1.500.000 Euros. There is an urgent need for availability of standardized global assay to monitor the rFVIIa treatment, which could contribute to constrain these prohibitive costs. *Blood Coagul Fibrinolysis* **25:518–521 © 2014 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

Blood Coagulation and Fibrinolysis 2014, **25**:518–521

Keywords: cyclophosphamide, haemophilia, inhibitors, intracranial haemorrhage, immunotolerance induction therapy, neurosurgery, retuximab, recombinant-activated FVII

[a]Thrombosis and Haemostasis Unit, Department of Translational Research and Laboratory Medicine, [b]Neurosurgery, Surgery Department, [c]Neuroradiology Unit, [d]Intensive Care Unit, Department of Emergency and Intensive care and [e]Clinical and Experimental Haematology Unit, Department of Haematology, Oncology and Stem Cell Transplantation, Giannina Gaslini Children's Hospital, Genova, Italy

Correspondence to Laura Banov, MD, Thrombosis and Haemostasis Unit, Department of Translational Research and Laboratory Medicine, Giannina Gaslini Children's Hospital, largo G.Gaslini 5, 16147 Genova GE, Italy
Tel: +390105636286; fax: +390105636421;
e-mail: laurabanov@ospedale-gaslini.ge.it

Received 27 September 2013 **Revised** 3 December 2013
Accepted 7 December 2013

Introduction

Alloantibodies to infused factor VIII remain the most challenging issue in the care of patients with congenital haemophilia A, who can experience life-threatening bleeding events. Inhibitor develops in about 30% of patients with severe haemophilia A [1].

Inhibitors eradication is targeted through strategies such as immunotolerance induction therapy (ITI), with frequent and regular administration of the missing factor, usually for months or years. Different ITI regimens have been used varying on the dose and frequency of FVIII infusions; the overall success rate is 63–80% with the median time to achieve tolerance ranging from 1.5 to 24 months, and higher doses seem to be more effective [2].

The treatment of bleeding episodes depends on the titre of inhibitor, the severity of the bleeding, and the anamnestic response. Bypassing agents such as recombinant-activated factor VII (rFVIIa) and activated prothrombin complex concentrates (aPCC) represent the only therapeutic drugs used for the management of bleeding in patients with high titre inhibitor [3].

rFVIIa overcomes inhibitor activity and induces haemostasis without need of factor VIII and IX, most probably through activation of extrinsic pathway and by enhancing the thrombin generation on the thrombin-activated platelet surface in the end leaning to the formation of a stable fibrin haemostatic plug [4]. Unlike aPCC, it carries no risk of blood-borne pathogen transmission [5]. It is licensed for use in congenital and acquired haemophilia (in patients with high antibody titres), FVII deficiency and Glanzmann's thrombaesthenia.

rFVIIa was first reported as a haemostatic agent in elective orthopaedic surgery in 1988 [6]. Since then, it has been widely used in patients with haemophilia complicated by inhibitors. In children, rFVIIa has been successfully used for bleeds either on demand and for prophylaxis in high titre inhibitor during ITI treatment [7]. Different schedules and dosages ranging from 90 to 300 μg/kg have been used in order to acutely manage bleeds and cover surgical procedures such as orthopaedic surgery [8–10]. Higher doses of rFVIIa seem to provide better response [2,11–13].

We report an urgent aggressive neurosurgery procedure for a life-threatening intracranial bleed in a 3-year-old boy with haemophilia A and high titre inhibitor, managed with tailored doses of rFVIIa.

Case report

L.R., a 3-year-old boy, was diagnosed with severe haemophilia A (FVIII:C < 1%) at 10 months. A stop codon mutation of the exone 9 (Gln429Stop) was detected.

0957-5235 © 2014 Wolters Kluwer Health | Lippincott Williams & Wilkins DOI:10.1097/MBC.0000000000000074

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After 10 exposure days to B domain-deleted recombinant FVIII (BDDrFVIII), a high titre inhibitor (20 BU) was detected.

In the following months, he presented with mild bleeding phenotype consisting of two joint bleeds, which required increasing rFVIIa doses, ranging from 90 to 150 μg/kg every 2 h to 270 μg/kg every 4 h to achieve complete resolution.

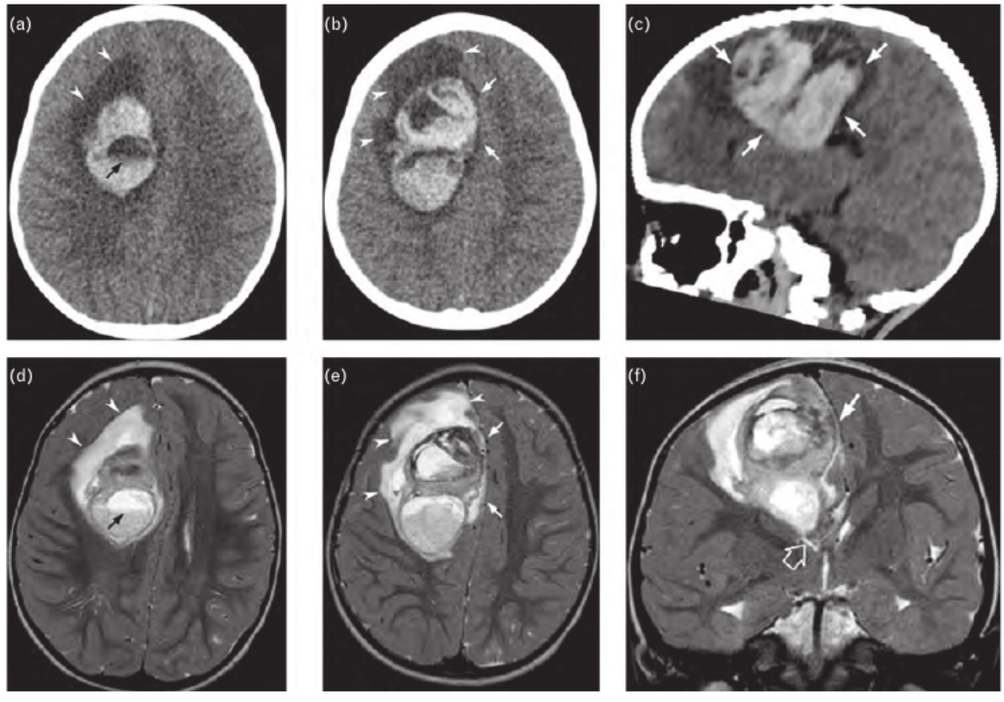
After 7 months of close observation, with a historical peak of 100 BU, ITI treatment was started with high daily doses of BDDrFVIII (150 IU/kg). To facilitate the administration of factor concentrate, a tunnelled central venous catheter was inserted; this procedure was successfully managed using rFVIIa, which was given at 270 μg/kg every 2 h for 24 h, then 150 μg/kg every 3 h the second day, and 90 μg/kg every 3 h the third day. After 9 months of ITI, because of lack of inhibitor titre reduction, we added immunosuppressive therapy with retuximab 375 mg/m^2 weekly for 4 weeks [14].

Two months after retuximab treatment, with inhibitor titre of 819 BU, the boy suddenly presented hemiplegia and loss of consciousness that rapidly turned into coma. He was, therefore, intubated in the emergency room and admitted to the intensive care unit. An MRI study of the brain showed a large intracranial bleed localized in the right frontal lobe with consequent shift of the median line and initial signs of intracranial hypertension (Fig. 1).

In this critical scenario, we opted for a life-saving attempt of removing the haematoma. The region and extent of craniotomy were guided by computed tomography (CT) scanning. A pressure transduction device for intra cranial pressure monitoring was placed in the parenchymal space, to maintain adequate cerebral perfusion pressure, oxygenation and metabolic substrate delivery, and to avoid cerebral herniation.

We started the procedure using mega doses of rFVIIa: preoperative bolus of 350 μg/kg repeated every 2 h for the first 4 days (total 60 mg/die). Intravenous tranexamic acid was associated.

Fig. 1



Brain CT (a–c) and MRI (d–f) performed at the onset. Axial nonenhanced CT images (a–b) and corresponding axial T2-weighted images (d–e) show a large hyperacute haemorrhage in the right frontal lobe with fluid-fluid level (black arrows) and surrounding oedema (arrowheads). Note the significant mass effect with midline shift (white arrows). Sagittal reconstructed CT image (c) shows the antero-posterior and cranio-caudal extension of the haematoma (white arrows). Coronal T2-weighted image (f) better depicts the shift of midline structures (white arrow) with transfalcine brain herniation (arrowhead) and compression of lateral ventricles (empty white arrow). CT, computed tomography.

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After neurosurgery, the patient's clinical conditions gradually improved. After 4 days, when the intracranial pressure catheter was removed, his neurologic conditions worsened again; he, therefore, underwent radiologic investigation (CT scan) showing re-bleeding of the same haemorrhagic lesion. At that time rFVIIa schedule was 270 μg/kg every 3 h (32 mg/die). We promptly increased the dosage and frequency of rFVIIa (350 μg/kg every 2 h) for 10 days, until neither clinical nor radiological progression of bleeding was observed. rFVIIa dose was then gradually tapered till the dose of 200 μg/kg every 12 h, which was maintained with the goal of preventing further bleedings. Table 1 summarizes rFVIIa doses adjustments.

Left side hemiplegia without cognitive disability was present.

At the same time, in order to reduce the inhibitor titre in this critical scenario, we started intravenous cyclophosphamide 10 mg/kg for five doses associated with oral rapamycin (immunosuppressant drug, which prevents activation of T cells and B cells by inhibiting their response to interleukin-2) [15,16] 3 mg/m^2. After the first cyclophosphamide cycle, the inhibitor titre decreased to 512 BU, but no further reduction was observed over 2 weeks; another cycle of intravenous cyclophosphamide was, therefore, administered. Subsequently, we performed maintenance therapy with four cycles of cyclophosphamide at 15 mg/kg given every 2 weeks. High-dose ITI (200 IU/kg) and rapamycin treatment were continued.

The inhibitor titre resulted 250 BU after 3 weeks. After 2 months of hospitalization, the boy was discharged with an intensive physiotherapy program. At 3.5 months from surgery, the inhibitor titre was 5 BU. An in-vivo recovery test showed 0,18 IU/ml FVIII activity 15 min after a bolus of 285 IU/kg BDDrFVIII, thus we stopped rFVIIa prophylaxis and increased the ITI regimen to 266 IU/kg daily targeting the major efficacy reported for higher doses [2] and to ensure more antihaemorrhagic protection during the intensive physiotherapy.

At 6 months from the event, the patient is able to use the left arm and to walk with parents' support with no cognitive and interaction impairment. He is still on ITI treatment (266 IU/kg per day), and combined immunosuppressant therapy with monthly retuximab 375 mg/m^2 and daily oral rapamycin therapy. The inhibitor titre is 2 BU.

Discussion

Rapidly expanding intracranial bleeds lead to coma and death; the only possible treatment is neurosurgical draining. However, neurosurgery requires effective haemostasis. In individuals with haemophilia and high titre inhibitors, clinical response to by-passing agents is highly variable, and the optimal rFVIIa dose for surgery remains to be established. High dose (150–200 μg/kg) seem to be equally safe and more effective in controlling bleeding than standard dose (90 μg/kg) [11]. On the contrary, continuous infusion of rFVIIa, which induces considerable savings eliminating unnecessary peaks [17], is reported to be associated to minor bleedings [11], and therefore still needs confirmation for the use in high-risk situation.

In this case, lower doses and continuous infusion were considered and excluded respectively for minimal bleeding risk [13], which was unfavourable in our scenario and for the lack of an approved protocol. Notably, a new bleeding arose on the fourth postoperative day when we tried to reduce the rFVIIa dose.

Common laboratory coagulation assays do not reflect the haemostatic activity of bypassing agents, and no validated assay is available to measure the in-vivo efficacy of these agents or predict individual patient response to treatment. Global haemostasis tests such as thrombin-generation assay and thromboelastography are considered capable to measure the in-vivo response to bypassing agents, but at present no standardized protocol has been defined [18]. Anyway, we could not perform global haemostasis assays, and rFVIIa treatment was monitored only with clinical and radiological follow-up.

For such high-risk procedure (neurosurgery in a high titre-high responder inhibitor patient), we thus decided to use very high doses of rFVIIa (350 μg/kg repeated every 2 h) targeting the maximum haemostatic potential, based on the previous successful experience of 270 μg/kg in managing minor surgery (catheter placement) and joint bleeds; as a result, the procedure was effective and uneventful. No side-effects were reported using rFVIIa.

In the literature, we found only one case report of a neurosurgery procedure in inhibitor adult patient,

Table 1 Recombinant-activated FVII tapering and prophylaxis in the postoperative period

	Rebleeding										
		↓									
	Postoperative day										
	1–4	5	6–15	16–18	19–21	22–24	25–27	28–30	31–33	34–36	37–101
rFVIIa dose (μg/kg)	350	270	350	350	214	214	270	214	270	214	214
Interval (h)	2	3	2	2	3	3	4	4	6	6	12

rFVIIa, recombinant-activated FVII.

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managed using doses of rFVIIa as high as 270 μg/kg every 2 h during the first 24 h [19]. To our best knowledge, there is no reported neurosurgery procedure in children with haemophilia and high titre inhibitor.

In conclusion, repeated mega doses of rFVIIa (350 μg/kg repeated every 2 h) were effective to safely control bleeding in a boy with 819 BU inhibitor with a deep and large intracranial haemorrhage who underwent urgent high-risk neurosurgery procedure, which saved his life.

We, therefore, believe that the therapeutic approach we used in this scenario with high doses of rFVIIa, which was effective and safe in our children, could be useful for other patients who face this critical situation.

Our experience outlines the success of a multidisciplinary team: the close and prompt collaboration between haematologist, neurosurgeon, and anaesthesiologist was successful in managing the critical haemorrhage without major sequelae and eradicating the inhibitor, at a cost of about 1.500.000 Euros, which could only be afforded in large tertiary care hospital of western countries; there is a urgent need for availability of standardized global assay to monitor the rFVIIa treatment, which could contribute to constrain these prohibitive costs.

Acknowledgements

Conflicts of interest

The authors declare there are no conflicts of interest.

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