INTEREST OF RECOMBINANT ACTIVATED FACTOR VII IN REFRACTORY IMMUNE THROMBOCYTOPENIA

INTERET DU FACTEUR VII ACTIVE RECOMBINANT DANS LA THROMBOCYTOPENIE

F. SAFI[1,4,*] ; M. HSAIRI[1,4] ;M. JMAL[2,4] ; M. ZRIBI[1,4] ; N. REKIK[2,4] ; L. GARGOURI[1,4] ; J. GARGOURI[3,4] ; I. BEN AMOR[3,4] ET A. MAHFOUDH[1,4]

1 : Service de pédiatrie, urgences et réanimation pédiatrique, CHU HédiChaker, Sfax-Tunisie
2 : Service d'urgence, CHU Habib Bourguiba, Sfax-Tunisie
3 : Centre CRTS, Sfax-Tunisie
4 : Faculté de médecine de Sfax, Université de Sfax, Sfax-Tunisie

***e-mail de l'auteur correspondant :** faizasafi@gmail.com

Abstract

We report the case of a 7-year-old girl with the history of chronic ITP who consulted for cataclysmic hematemesis.
Corticosteroids (methylprednisolone IV 30 mg/kg), intravenous immunoglobulin (2g/kg) were administered urgently with red blood cells (20 ml/kg) and platelets transfusion. However, the abundant digestive hemorrhage recurred with the installation of shock syndrome. The use of catecholamine (noradrenalin 0.5gamma/kg) was necessary.
Life threating of the young child was committed so we opted for the use, as an ultimate resort, of the recombinant activated factor VII at the dose of 120 µg/kg spaced 3 hours apart. A rapid and favorable evolution was noted, marked by the stabilization of the hemodynamic state, the drying up of the hemorrhage from the first dose of recombinant activated factor VII and the maintenance of a stable platelet's count at 181 X10(9)/L. No side effects were observed. Follow-up was satisfactory.

Key - words: Hemorrhage; Immune thrombocytopenia; Recombinant activated factor VII.

Résumé

Nous rapportons le cas d'une fillette de 7 ans présentant des antécédents de purpura thrombopénique chronique qui avait consulté pour une hématémèse cataclysmique. Des corticostéroïdes (méthylprednisolone IV à 30 mg / kg), des immunoglobulines intraveineuses (2 g / kg) ont été administrés en urgence avec des globules rouges (20 ml / kg) et une transfusion de plaquettes. Cependant, l'évolution était marquée par la récidive de l'hémorragie avec l'installation d'un état de choc. Le recours aux catécholamines (noradrénaline 0,5 g / kg) était nécessaire. Devant l'état critique de l'enfant, nous avons utilisé le facteur VII activé recombinant à la dose de 120 µg / kg, espacés de 3 heures. Une évolution rapide et favorable a été observée, marquée par la stabilisation de l'état hémodynamique, le tarissement de l'hémorragie dès la première dose de facteur VII activé recombinant et le maintien d'une numération plaquettaire stable à 181 X 10 (9) / L. Aucun effet secondaire n'a été observé. Le suivi était satisfaisant.

Mots clés : Hémorragie ; Thrombocytopénie immunologique ; Intérêt du facteur VII activé recombinant.

ملخص

قمنا بدراسة حالة فتاة تبلغ من العمر 7 سنوات ولديها سابقة مرضية من نوع فرفرية نقص الصفيحات المزمن و التي استشارت لعلاج نزيف الدم الوخيم.
كانت تدار الستيرويدات القشرية (IV ميثيل بريدنيزولون 30 مغ / كغ) ، الغلوبولين المناعي الوريدي (2 جم / كجم) على وجه السرعة مع خلايا الدم الحمراء (20 مل / كغ) ونقل الصفائح الدموية. ومع ذلك ، تميز التطور بتكرار النزيف مع تثبيت حالة الصدمة. كان من الضروري استخدام الكاتيكولامينات (بافراز 0.5 غ / كغ).
بالنظر إلى الحالةالحرجة للبنية، استخدمنا العامل المنشط المؤتلف السابع بجرعة 120 ميكروغرام / كيلوغرام ، متباعدة 3 ساعات. ولوحظ تطور سريع ومواتي ، تميز باستقرار الحالة الديناميكية الدموية ، وتجفيف النزف عند الجرعة الأولى من العامل المنشط المؤتلف السابع والحفاظ على عدد الصفائح الدموية المستقر عند 181 في 10 (9) / ل. لم نلاحظ من حينها تأثير جانبي ثم كانت المتابعة للمريضة بصفة عادية.

الكلمات المفاتيح : النزيف ; نقص الصفيحات المناعي ; فائدة العامل المنشط المؤتلف السابع.

INTRODUCTION

Recombinant activated factor VII (r FVIIa) is a pro haemostatic agent originally developed for the treatment of bleeding in patients with hemophilia A and B [1,2]. It is proven effective in other constitutional diseases of homeostasis (Glanzmann's Thrombasthenia, Factor VII deficiency)[3]. Its contribution has been confirmed in the prevention of hemorrhages occurring during surgical acts or invasive procedures for this group of patients. However, its use is poorly documented in the control of bleeding secondary to homeostasis disorders due to immune thrombocytopenia (ITP)[4,5] especially in children. We report the case of reversible hemorrhagic shock following the administration of recombinant activated factor VII in a girl with ITP.

CASE REPORT

A 7-year-old girl has been diagnosed refractory chronic ITP since the age of three and a half-year. Etiological explorations (viral serology, rheumatoid factor, anti-nuclear antibodies, complement and immune checkpoint) were negative. Several therapies have been tried such as corticosteroids, intravenous immunoglobulin and then immunosuppressive drugs but failed to rise up platelet's count. Although splenectomy was indicated, it was not conducted because of the chronic low level of platelets under $50x10^9$/L.

For this current episode, she consulted for cataclysmic hematemesis. At physical examination, she has tachycardia (146 beats per minute) with a blood pressure of 100/60 mmHg, petechial purpura in both lower limbs and abdomen. There was no neurological or respiratory distress. The blood count showed thrombocytopenia at 4 $x10^9$/L, leukocytosis at 12 150 per mm3 with 9.9g/dl of hemoglobin. Prothrombin ratio was normal (69%).

Urgently, corticosteroids (methylprednisolone IV 30 mg/kg over 1 hour) and intravenous immunoglobulin (2g/kg with the first bottle over 4 hours and the rest during 12 hours) were administered concomitantly. Red blood cells (20ml/kg) and platelets (1 unit per 5 kg) were transfused.

However, the abundant digestive hemorrhage recurred within four hours after admission with the installation of shock syndrome. The use of catecholamine (noradrenalin 0.5gamma/kg) was necessary.

Life threating of the young child was committed so we opted for the use, as an ultimate resort, of the recombinant activated factor VII at the dose of 120microgramme/kg spaced 3 hours apart. A rapid and favorable evolution was noted from the first dose of recombinant activated factor VII. It was marked by the stabilization of the hemodynamic state, the drying up of the hemorrhage. No side effects were observed. Platelet's count rose progressevely to $50x10^9$/L 12 hours after admission then to $181x10^9$/L 24 hours after.

Home discharge was possible after one week of hospitalization without any recurrence of hemorrhage. The oesogastroduodenal fibroscopy performed remotely did not show any anomaly. Splenectomy was performed later and level of platelets rose to $150x10^9$/L. Follow-up was satisfactory clinically and biologically with a persistent stable platelet's count after 18 months of hindsight.

DISCUSSION

Our case reports the benefit of using recombinant activated factor VII in uncontrolled bleeding episodes in ITP patients. Recombinant activated factor VII seems to be effective and fast in case of failure of conventional treatment to stop bleeding.

Factor VII is a serine protease belonging to the family of coagulation proteases whose synthesis is dependent on vitamin K. The activated form results from cleavage of factor VII at a specific peptide bridge [2,5]. The final form (recombinant activated factor VII (rFVIIa)) can be produced by genetic engineering following specific insemination and purification series [2].

RFVIIa initiates homeostasis at a vascular breach to form complexes with tissue factor (FT) located on the surface of endothelial cells. The rFVIIa / FT complex produces a small amount of thrombin that allows platelet activation. In addition, rFVIIa activates FX in FXa on the surface of activated platelets. FXa then allows the activation of prothrombin (FII) thrombin (FIIa) which will then convert fibrinogen to fibrin, thus allowing the formation of a stable fibrin clot at the site of the vascular lesion [2,6](figure1).

The indications for using rFVIIa are various. In constitutional and acquired hemophilia, rFVIIa has proved its effectiveness especially in emergency situations with heavy bleeding. The chances of success in these situations are of the order of 80 to 90% [7,8].

The second indication for rFVIIa is Glanzmann Thrombasthenia. It is a constitutional thrombopathy caused by a deficit in platel

et GPIIb/ IIIa receptor whose risk of bleeding is very important. The main series on the subject included 59 patients (with 108 acute severe bleeding episodes) and showed rFVIIa efficacy in 64% of cases [8].

Various other pathologies have been described in the literature where the use of rFVIIa significantly decreased or stopped bleeding a few minutes after injection. Transfusion requirements have also been significantly reduced in these series [9]. In uncontrolled alveolar hemorrhage, rFVIIa is proposed as a life-saving treatment in a patient with leukemia and other Wegener's disease [10].

The recommended dose is 90 µg / kg body weight in one IV bolus injection, repeated at a dose of 60 to 120 µg / kg each two to three hours later if necessary [7, 8].

The clinical efficacy of rFVIIa was also evaluated in about sixty patients with FVII deficiency, for various types of bleeding events and in surgery. This efficacy has been observed during curative treatment and prevention of hemorrhagic risk in surgery or when performing invasive procedures [11].

In our case, digestive hemorrhage was severe with hemodynamic resounding. For the level of platelets, there was no response to conventional treatment (transfusion, corticosteroids, veinoglobulins). RFVIIa (Novoseven®), the last resort treatment succeeded to stop rapidly bleeding, to dry up the hemorrhage and to save the patient.

The use of rFVIIa in case of idiopathic thrombocytopenic purpura is not consensual.

In the rare cases reported, it is reserved for exceptional forms with immediate life-threatening, or in case of operative indication [12]. Indeed, its effectiveness has been proved in the reduction of intra-cerebral hemorrhage in a 16-year-old child with refractory ITP [4]. It has also been used preventively during the splenectomy in another case of ITP [2].

Thrombotic events with recombinant activated factor VII (rFVIIa) are rare and associated with older age, cardiovascular disease, and concomitant use of activated prothrombin complex concentrates [18].

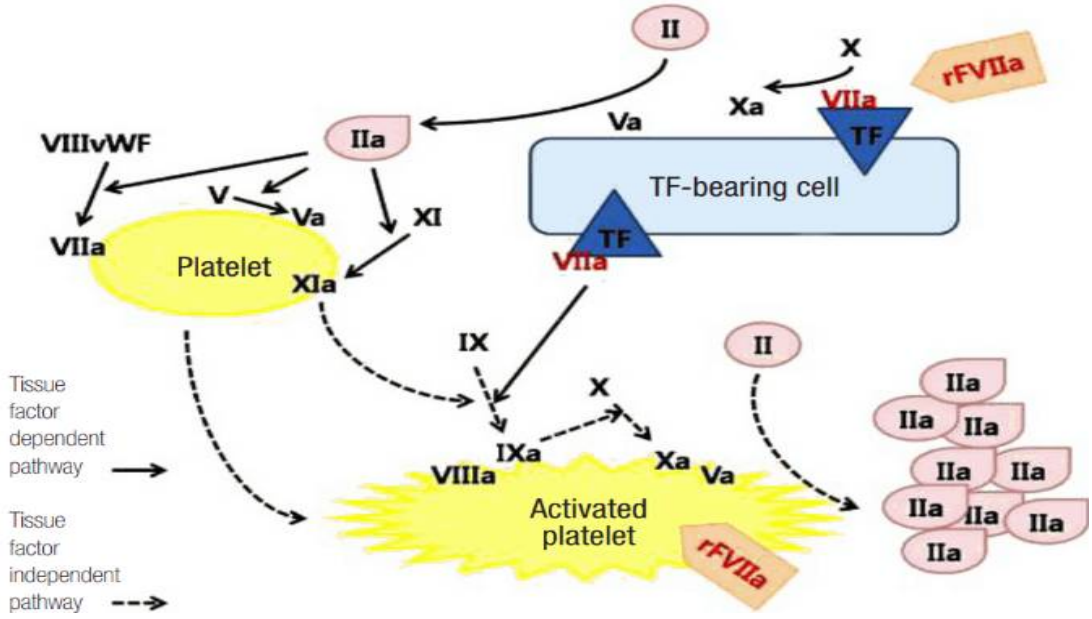

Figure 1: Mechanism of action of RFVIIa [6].
RFVIIa: Recombinant activated factor VII.

CONCLUSION

Recombinant coagulation factor VIIa (rFVIIa) seems to be an effective and promising treatment for uncontrollable hemorrhage in ITP patients. Several published cases had shown its success, but we need more studies to prove the efficacy, the safety and the therapeutic protocols in this category of patients.

REFERENCES

[1] Erhardtsen E. Ongoing NovoSeven ® trials. Intensive Care Med. 2002 ;28(0):s248- 256.

[2] Boyerneumann C, Mercier F, Veyradier A. Facteur VII active recombinant (NovoSeven®): indications et limites. Réanimation. 2006;15(7-8):576-583.

[3] Agence nationale de sécurité du médicament et des, produits de santé (ANSM). Protocole de suivi des patients traités par NovoSeven (Eptacog alfa activé) pour le « traitement prophylactique chez l'hémophile A ou B avec inhibiteurs », hors situations d'interventions chirurgicales et/ou procédures invasives et lorsqu'il n'y a aucune alternative thérapeutique. 2017.

[4] Barnes C, Blanchette V, Canning P, Carcao M. Recombinant FVIIa in the management of intracerebral haemorrhage in severe thrombocytopenia unresponsive to platelet-enhancing treatment. Transfus Med Oxf Engl. 2005;15(2):145-150.

[5] Wróbel G, Dobaczewski G, Patkowski D, Sokół A, Grotthus E. Experiences with recombinant activated factor VII in the treatment of severe refractory thrombocytopenia. Pediatr Blood Cancer. 2006;47(5 Suppl):729-730.

[6] Park SC, Yeom SR, Han SK, Jo YM, Kim HB. Recombinant Activated Factor VII as a Second Line Treatment for Postpartum Hemorrhage. Korean J Crit Care Med. 2017 ;32(4):333-339.

[7] Arkin S, Cooper HA, Hutter JJ, Miller S, Schmidt ML, Seibel NL, et al. Activated recombinant human coagulation factor VII therapy for intracranial hemorrhage in patients with hemophilia A or B with inhibitors. Results of the novoseven emergency-use program. Haemostasis. 1998;28(2):93- 98.

[8] Liebman HA, Chediak J, Fink KI, Galvez AG, Shah PC, Sham RL. Activated recombinant human coagulation factor VII (rFVIIa) therapy for abdominal bleeding in patients with inhibitory antibodies to factor VIII. Am J Hematol. 2000;63(3):109-113.

[9] Martinowitz U, Michaelson M, Israeli Multidisciplinary rFVIIa Task Force. Guidelines for the use of recombinant activated factor VII (rFVIIa) in uncontrolled bleeding: a report by the Israeli Multidisciplinary rFVIIa Task Force. JTH. 2005;3(4):640-648.

[10] Dabar G, Harmouche C, Jammal M. Efficacité du facteur VII activé recombinant dans l'hémorragie alvéolaire diffuse. Rev Mal Respir.2011;28(1):106-111.

[11] Commission de transparence. Novosen. Haute Autorité de Santé; 2004. disponible à l'URL https: //www.has-sante.fr/jcms/c_245508/fr/avis-medicament-ct031720-pdf (consulté le 19 octobre 2019)

[12]www.orpha.netdatapathoProfrUrgences_Purpurathrombopeniqueimmunologique-frPro3002.pdf.pdf.

[13] Rajpurkar M, Croteau S, Boggio L, Cooper D, Thrombotic events with recombinant activated factor VII (rFVIIa) in approved indications are rare and associated with older age, cardiovascular disease, and concomitant use of activated prothrombin complex concentrates (aPCC), Journal of Blood Medicine 2019:10 335–340.