

Efficacy and safety of recombinant factor VIIa in the treatment of bleeding episodes in patients with aplastic anemia

A. M. AL HAMMADI* and S. SALLAH†

*Department of Hematology, Bone Marrow Transplantation Center, University of Baghdad, Iraq; and †Novo Nordisk A/S International Operations, Athens, Greece

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Aplastic anemia is characterized by severe compromise of hematopoiesis and by a hypocellular bone marrow [1]. Hemorrhagic episodes in patients with aplastic anemia occur usually secondary to thrombocytopenia and require frequent support with platelet concentrates and other blood products. Repeated transfusion often results in alloimmunization and lack of increments to further platelet transfusion, and increases the demand load on transfusion centers.

Activated recombinant factor VII (rFVIIa, NovoSeven®; Novo Nordisk A/S, Bagsvaerd, Denmark) has been used to control bleeding episodes in a wide spectrum of congenital and acquired bleeding disorders [2]. In this letter, we describe our experience in the management of hemorrhagic episodes in patients with aplastic anemia and severe thrombocytopenia.

Over the past two years, seven patients with aplastic anemia and thrombocytopenia have been treated in our institution for a variety of bleeding episodes. The etiology of aplastic anemia was autoimmune in two patients and idiopathic in five patients. The platelet counts in these patients ranged between 2000 and 10 000 per microliter at the time of admission. A total of 17 bleeding episodes were observed, which consisted of nine vaginal bleedings grade IV (> three vaginal packs over 24 h), seven episodes of epistaxis grade III (anterior packing) to grade V (no response to any measure), and one episode of hematuria grade III (passage of clots with urine).

All patients received rFVIIa at a dose of 90 mcg kg⁻¹ after failure of platelet concentrates to achieve adequate hemostasis (10 bleeding episodes) or lack of availability of apheresis platelets (seven bleeding episodes).

Bleeding was controlled in all patients after an average of two doses (range of one to three doses), and approximately 10–25 min after the administration of rFVIIa. The interval of administration of rFVIIa in patients requiring more than a single dose to achieve hemostasis was 2–3 h. The requirements for blood products were reduced from an average of four units of platelets (range of three to six units) and three units

of red blood cells (range of two to five units) prior to rFVIIa, to zero to one units of red blood cells and no further requirements for platelets following rFVIIa. No adverse events were observed.

The use of rFVIIa in patients with thrombocytopenia and underlying benign and malignant disorders has been previously described [3–7]. However, to our knowledge, this current report is the first description of a case series on the administration of rFVIIa in patients with aplastic anemia.

In a cell-based *in vitro* model of thrombocytopenia, it was demonstrated that rFVIIa increases the efficiency of thrombin generation [8,9]. Even in the presence of low platelet number, thrombin-activated platelets appear to provide sufficient surface to bind FXa and FVa to form the prothrombinase complex [8]. The prothrombinase complex can catalyze the conversion of large amounts of prothrombin to thrombin, which subsequently converts fibrinogen to fibrin. In addition, recently, it has been shown that rFVIIa enhances platelet adhesion and deposition to fibrinogen and collagen, which may compensate for the reduced platelet count [10].

Although the current experience is based on a small number of patients, our results provide supportive evidence of the efficacy and safety of rFVIIa in patients with thrombocytopenia. The dose used in our patients (90 mcg kg⁻¹) is based on the experience in hemophilic patients. It is worth noting that the administration of two doses only of rFVIIa was sufficient to control the bleeding episodes, regardless of severity, in all patients in this series and without any safety issues. Based on the current experience, we propose the use of rFVIIa in patients with aplastic anemia and bleeding episodes refractory to platelet transfusion or as a substitute for platelets due to lack of blood products.

Disclosure of Conflict of Interests

Sabah Sallah is an employee of Novo Nordisk A/S.

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Correspondence: Sabah Sallah, Novo Nordisk A/S International Operations, Athinas Avenue and Areos 2a, Athens, 16671, Greece.
Tel.: +30 6948620906; fax: +30 210 9670663; e-mail: asll@novonordisk.com

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The phosphodiesterase 4D gene for early onset ischemic stroke among normotensive patients

H.-F. LIN,^{*†‡} Y.-C. LIAO,[§] C.-W. LIOU,[¶] C.-K. LIU^{*†} and S.-H. H. JUO^{§**††}

^{*}Department of Neurology, Kaohsiung Medical University Hospital, Kaohsiung; [†]Department of Neurology, Kaohsiung Medical University, Kaohsiung; [‡]Department of Neurology, Kaohsiung Municipal Hsiao-Kang Hospital, Kaohsiung Medical University, Kaohsiung; [§]Graduate Institute of Medical Genetics, Kaohsiung Medical University, Kaohsiung; [¶]Department of Neurology, Kaohsiung Medical Center, Chang Gung University College of Medicine, Kaohsiung; ^{**}Department of Clinical Research, Kaohsiung Medical University Hospital, Kaohsiung; and ^{††}Department of Medical Research, Mackay Memorial Hospital, Taipei, Taiwan, China

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The phosphodiesterase 4D (PDE4D) gene was recently reported as a risk gene for stroke [1]. Although several studies tried to replicate the results, only one study focused primarily on early onset stroke [2], where the study subjects were Caucasian women and African-American women. Our aim was to study four commonly investigated single nucleotide polymorphisms (SNPs) of the PDE4D gene in young stroke subjects recruited in southern Taiwan. In addition, we stratified the subjects based on the presence of hypertension because two studies reported that the PDE4D genetic effect is more significant in non-hypertensive subjects [3,4]. An interaction between the gene and smoking was also explored in the present study.

The patients in the present genetic study were primarily from the Southern Taiwan Young Stroke Study [5]. Our patients

Correspondence: Suh-Hang H. Juo, Kaohsiung Medical University, 100 TzYou First Road, Kaohsiung City 807, Taiwan, China.
Tel.: 886 7 312 1101 ext. 6470; fax: 886 7 321 3931; e-mail: shj34@columbia.edu

[†]These authors contributed equally to this work.

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included 57 cases of large-artery atherosclerosis, 18 cases of cardioembolism, 66 cases of small-vessel occlusion, 16 cases of other determined etiology, and 33 cases of undetermined etiology. Two hundred and eleven stroke-free participants were recruited from the general population between 2002 and 2006. We selected four SNPs that have been implicated to be associated with stroke: rs12188950 (i.e. SNP45, indicated in the original article [1]); rs702553 (SNP56); rs966221 (SNP83); and rs2910829 (SNP87). Polymorphisms were genotyped using TaqMan[®] technology (Applied Biosystems, Foster City, CA, USA). Each SNP was in Hardy-Weinberg equilibrium for cases and controls. SNP45 was monomorphic in our population.

For SNP56, the results indicated that genotypes TT [crude odds ratio (OR) = 2.0, $P = 0.014$] and AT (crude OR = 1.4, $P = 0.157$) carried a higher risk than the reference AA genotype (Table 1). It appeared that the T allele had an additive effect, and thus we used the additive model to estimate adjusted OR. After adjusting for significant covariates including diabetes, hypertension, and current smoking, the OR was 1.36 ($P = 0.052$). The final multivariate regression model suggested that smoking, diabetes and hypertension were the major risk factors for early onset stroke. Further analysis according to the hypertensive status found that the genetic