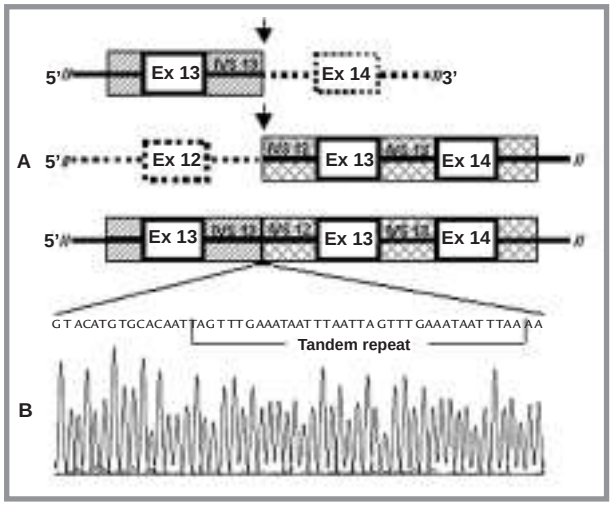

Figure 1. Schematic representation of exon 13 duplication. (A) The location of exon 13 in two misaligned X-chromosomes is shown. The crossing over (// = break points) between non-homologous regions creates a recombined chromosome with two exons 13 duplicated in frame. (B) The new sequence originating from the rearrangement, which includes the breakpoint, can be seen. The AT rich sequence, which is normally present in intron 12, appears to be tandemly repeated, in patients with the mutation.

ing using PCR-sequencing of the essential region of the FVIII gene on genomic DNA leaves some gene alterations undetected. Secondly, it is possible that the high frequency of this mutation is the result of a founder effect although it will be essential to study a broader population of mild HA patients from central and southern Italy in order to unravel this matter. Since 3/10 patients were born outside our region, we believe that the first mutation we should look for in Italian patients with mild HA is duplication of exon 13.

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Acknowledgments: The authors wish to thank Mrs. Barbara Caruzzo for her excellent assistance in preparing the letter. This work was supported in part by the Compagnia di S. Paolo and by Fondazione Carige.

Key words: hemophilia A, mutation, exon 13.

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Disorders of Hemostasis

Treatment of acquired factor VIII inihibitor with recombinant activated factor VIIa: data from the Italian registry of acquired hemophilia

We report on the data collected in the Italian Registry of acquired haemophilia (AH) in 2001. Recombinant activated factor VII (rFVIIa) was selected as first-line therapy in 19 bleeding episodes because of their severity and as salvage in one case. Bleeding was controlled in 90% of the episodes, indicating the efficacy of rFVIIa in HA.

haematologica 2004; 88:759-761
(*http://www.haematologica.org/journal/2004/6/759*)

Acquired hemophilia (AH) is a rare syndrome caused by inhibitors to factor VIII (rarely to factor IX), characterized by the sudden onset of bleeding, usually severe, in patients with no family or personal history of bleeding diatheses.[1,2] It is a medical emergency, requires prompt treatment and is clinically and financially demanding. Various therapies can be used: human or porcine FVIII, DDAVP, immunoglobulins, activated prothrombin concentrate, immunoadsorption and recombinant activated factor VII (rFVIIa). The available data are from anecdotal case reports and retrospective studies with a limited number of patients; none of the available agents is effective in all the patients. rFVIIa, a systemic hemostatic agent with topical action, is beneficial in a variety of bleeding conditions: hemophiliacs with inhibitor, elective surgery (prostatectomy, hepatectomy, liver transplantation), hereditary platelet disorders, and severe bleeding secondary to oral anticoagulation and trauma.[3,4]

The multicenter study by Hay *et al.* on the use of the rFVIIa is the largest so far reported.[5] Our study is a retrospective analysis of the patients reported to the Italian registry in 2001 (*www.emonet.org*) who were treated with rFVIIa. The following information was requested: primary condition, cause of bleeding or its spontaneous occurrence, site, severity evaluated by the hemoglobin level and by transfusion requirements, inhibitor titer, therapy, selection criteria and results. The clinical response was evaluated by the patient's physician at 6, 12, 24 and >24 hours and was scored as very effective (complete cessation of bleeding), effective (residual minor bleeding), partially effective (reduced but still significant bleeding); ineffective. Any adverse event occurring within two months of the end of treatment was recorded. Twenty-eight new patients were registered, 15 of whom were treated with rFVIIa, 11 with other modalities, and 2 who did not require treatment (Table 1). rFVIIa was selected as first-line treatment in 19 bleeding episodes because of the severity of the episode and as salvage treatment in case 1 (Table 2). The median total dose to control the bleeding (primary end-point) in groups treated with bolus or continuous infusion was 309 and 474.5 μg/kg, respectively, with a wide range. One patient concomitantly received tranexamic acid. Treatment was very effective or effective in 13/15 patients (86.6%) and in 18/20 bleeding episodes (90.0%), within 24 (14 episodes) and 48 hours (4 episodes), including the recurrences. There were no differences between the groups treated with intermittent or continuous infusion (*data not shown*). Treatment was scored par-

Table 1. Clinical characteristics of the patients treated with rFVIIa.

Number	15
Sex (M/F)	9/6
Age (median and range)	72 (62-81)
Idiopathic	12
Secondary*	3
Number of treatments	23
coverage of procedures°	3
spontaneous bleeding	17
induced bleeding#	3
Bleeding site	
muscle hematoma	11
skin	7
hemarthroses	1
hemothorax	1
Hb (g/dL)§	8 (6.5-10.4)
Inhibitor BU/mL§	15 (2.5-323)
RBC units requirement§	4.5 (1-9)
Transfused patients (number)	10/15

**Autoimmune thyroiditis, myelodysplastic syndrome, breast cancer. °CVC positioning, hemothorax evacuation, mastectomy. #venipuncture/i.m. injection 2; trauma 1. §Median value and range*

Table 2. rFVIIa treatment of bleeding episodes (median and range); the 3 surgical procedures were not included in the analysis.

	Bolus	*Continuous infusion*
Patients	8	7
Number of treatments	10	10
Initial dose (μg/kg)	90 (46-118)	98 (72-124)
Successive doses (μg/kg)	90 (46-90)	95 (15-30)*
Dose to control bleeding (μg/kg)	309 (46-1,568)	474.5 (266-530)
Time interval (hours)	2-6	–
Number of doses°	10 (1-60)	–
Days of treatment°	2.75 (0-8)	4 (1.5-15)

**mg/kg/h; °additional treatment given according to the clinical judgment.*

tially effective in 1 patient (2 red cell units transfused in the following 2 days) and ineffective in one patient who died of bleeding. The procedures (not included in the analysis) were uneventful. Bleeding recurred spontaneously in 5 patients (2, 3, 8, 12 and 30 days after discontinuation of rFVIIa) in the same site in 4 patients and in the pleural space in one patient who had undergone thoracentesis. Four deaths unrelated to bleeding occurred: two patients died of an underlying neoplasia (breast cancer and myelodysplasia) and two patients who had previously had by-pass surgery died of their cardiovascular conditions 9 and 40 days after discontinuation of rFVIIa. No thromboembolic events occurred during or in the immediate period after treatment. The majority of the investigators chose rFVIIa as first-line treatment because of the severity of bleeding. Ten patients required blood transfusions. The range of the inhibitor titer within the whole group was wide and was not related to bleeding events. Published guidelines specify that rFVIIa is not first line treatment in patients with low titer inhibitors.[6,7] Our report and that of Hay agree on the rapidity of the control of bleeding achieved with rFVIIa. Similar observations were reported by other investigators.[8,9] If future studies confirm this speed of action, perhaps with lower doses, the indications for rFVIIa in AH may be reconsidered, also in the context of the controversy on the relationship between inhibitor titer and severity of bleeding.[7,10] An early response is predictive of the overall response and alternative therapy should be considered in the case of initial unresponsiveness.

The treatment was safe, being without side effects or thromboembolic complications. Systemic administration of rFVIIa carries a very low risk of thromboembolism. In 6,500 patients with hemophilia or other bleeding disorders, treated from 1996 to October 2001 with more than 480,000 standard doses, only 17 thromboembolic events were reported but their relation to treatment was doubtful either because of the time-event relation or the presence of predisposing co-morbid conditions (diabetes, atherosclerosis, hypertension).[3] The absolute number of patients with AH is low (1 × million population per year) but the mortality rate from bleeding is high (7.9-22%). These points should be considered in the future evaluations of the cost/benefit ratio of rFVIIa treatment.

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Key words: acquired hemophilia; bleeding; rFVIIa therapy.

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