Clinical use and the Italian demand for activated prothrombin complex and activated recombinant factor VII concentrates

Antonio Coppola[1], Annarita Tagliaferri[2], Gabriele Calizzani[3], Fabio Candura[3], Massimo Franchini[4], Carlo Ruosi[1], Giuliano Grazzini[3], Giovanni Di Minno[1]

[1]Regional Reference Centre for Coagulation Disorders, Federico II University Hospital, Naples; [2]Regional Reference Centre for Inherited Bleeding Disorders, University Hospital, Parma; [3]Italian National Blood Centre, National Institute of Health, Rome; [4]Department of Haematology and Transfusion Medicine, Carlo Poma Hospital, Mantua, Italy

Introduction

The activated prothrombin complex concentrate (aPCC, Factor Eight Inhibitor Bypassing Activity, FEIBA, Baxter, Deerfield, IL, USA) and the recombinant activated factor VII concentrate (rFVIIa, NovoSeven, Novo Nordisk A/S, Bagsværd, Denmark) are the so-called "by-passing agents", i.e. products able to promote haemostasis through mechanisms alternative to the physiological tenase complex, in which a phospholipid-dependent reaction occurs with factor (F) X as the substrate, activated (a) FIX as the enzyme and FVIIIa as a cofactor[1]. The mechanism(s) of action of these agents are still not completely elucidated. The aPCC, which contains activated FII, FIX, FX and small amounts of FVII, is thought to facilitate thrombin generation on the platelet surface. This product was first introduced in clinical practice in 1975, as a therapeutic agent for haemophilia B when specific FIX concentrates were not available, and in the current vapour-heated formulation in 1985[2]. The rFVIIa concentrate was specifically developed to provide a therapeutic approach in haemophilia with inhibitors, being able at high concentrations to enhance platelet-surface FXa generation, irrespective of the presence of FVIII or FIX[3]. The first use of rFVIIa was reported in 1988, and the product was registered in Europe in 1996 and in the United States in 1999.

aPCC and rFVIIa are the mainstay of treatment of patients with congenital and acquired haemophilia (AH) with inhibitors[4-6], in whom efficacy and safety of such agents have been documented over more than three and two decades of clinical use, respectively. As a specific replacement agent, rFVIIa is indicated in patients with factor VII deficiency[7] and, as an alternative haemostatic agent, in patients with Glanzmann's thrombasthenia (GT) and alloantibodies and/or platelet transfusion refractoriness[8].

Because of the rarity of the other recognised indications for treatment, most clinical and literature data regarding bypassing agents have been generated in the setting of congenital haemophilia with inhibitors. Before presenting the Italian demand for aPCC and rFVIIa in this 5-yr analysis, the clinical use of bypassing agents in the management of patients with bleeding disorders, in particular in those with congenital haemophilia and inhibitors, with the numerous challenges and open issues, will be concisely reviewed.

Bypassing agents in the management of congenital haemophilia with inhibitors

Approximately 30% of previously unexposed patients (PUPs) with severe haemophilia A (FVIII <1%) generate inhibitors, typically during the first 20-50 exposure days to FVIII concentrates, as a result of a complex process in which multiple genetic and environmental factors interplay[9]. Inhibitor incidence is lower in patients with severe haemophilia B (FIX <1%) and in those with moderate (FVIII/IX 1-5%) or mild (FVIII/IX >5-40%) haemophilia. According to the highest documented inhibitor level and, particularly, to the presence of anamnestic response at factor concentrate re-exposure, high-responding (HR, >5 BU mL^{-1}) or low-responding (LR, always <5 BU mL^{-1}) inhibitors are distinguished. In some patients, inhibitors are detected temporarily, and are no longer found on replacement treatment (transient inhibitors). Inhibitors are transient or LR in about half of PUPs[10].

The development of a specific inhibitor to FVIII or FIX results in the partial or complete lack of efficacy of factor concentrates. Although bleeding frequency is not higher in inhibitor patients[11], bleeding may be severe and, particularly in HR patients, achieving haemostasis for bleeding episodes or in occasion of invasive procedures is often more difficult than in non-inhibitor haemophiliacs. In patients with LR inhibitors bleeding episodes may be managed by increased FVIII/FIX dosages, able to overcome the interference of inhibitors. The same approach may be reserved to severe bleeds in patients with HR inhibitors but low actual titre, before the elicitation of the anamnestic response. However, in the majority of cases bypassing agents, aPCC or rFVIIa, are needed in patients with HR inhibitors[4,5,12]. More recently, increasing data regarding the efficacy of prophylactic

regimens with both by-passing agents have been achieved[13-15]. However, the ultimate goal of management of these patients is the eradication of inhibitors, enabling to restore the standard safe and effective replacement treatment, in particular the feasibility of prophylaxis in children, in order to avoid or reduce the enhanced long-term morbidity due to haemophilic arthropathy and the deterioration of quality of life[16]. Immune tolerance induction (ITI) by means of frequent and long-term administration of factor concentrates is presently the only strategy proven to eradicate inhibitors, although the optimal modality of such treatment is still debated[17,18]. ITI is attempted in most haemophilia A inhibitor patients, particularly in children with recent-onset inhibitors. Management of inhibitors in haemophilia B is more challenging, as re-exposure to FIX may be complicated by severe anaphylactoid reactions and nephrotic syndrome, thus limiting recommendation for ITI in this setting[17,19]. ITI fails in approximately 30% of cases, therefore prevention and treatment of bleeding rely on bypassing agents in these patients, together with those waiting for or not candidate to inhibitor eradication.

Characteristics and regimens of treatment of aPCC and rFVIIa are summarised in Table I. Clinical studies, in most cases retrospectively, demonstrated the effectiveness of both agents in achieving haemostasis in more than 90% of surgical procedures and in more than 80% of bleeding episodes, even in the setting of home-treatment[1-3,19-28]. As regards rFVIIa, comparable efficacy and safety of single high-dose (270 μg kg^{-1}) *vs* repeated standard doses (90 μg kg^{-1}) have been reported, thus high-dose regimen may be conveniently used in patients necessitating intensive treatment and in children with venous access problems. Many clinicians tend to prefer rFVIIa in paediatric patients because of its recombinant origin and the lack of traces of FVIII or FIX potentially inducing an anamnestic response in children candidates to ITI. However, no general recommendations are possible for clinical choices in the management of bleeding episodes in inhibitor patients. Some patients may respond more efficaciously to rFVIIa and others to aPCC, moreover the same patient may achieve a better response to one product or to the other in different occasions. Few studies evaluated the comparative efficacy of aPCC *vs* rFVIIa and the first head-to head prospective trial (the FEIBA NovoSeven comparative study, FENOC) confirmed such a variability of response to treatment. The two treatments (a single dose of FEIBA, 75-100 I.U. kg^{-1}, or two doses of rFVIIa, 90-120 μg kg^{-1}, used alternatively in 2 joint bleeding episodes) showed substantially similar efficacy (approximately 80%), although statistical requirements for equivalence were not met. However, more discordant responses than expected (response to one agent *vs* the other for bleeding episodes within the same patients) were reported[29]. A global efficacy algorithm taking into account pain and mobility scores at 9 hours after the start of treatment and the requirement for additional haemostatic agents were considered in the other available head-to-head randomised trial. No statistically significant differences were found in the global algorithm, or in pain and mobility scores measured separately. A significantly lower percentage of patients in the rFVIIa 270 μg kg^{-1} group, but not in those receiving 3×90 μg kg^{-1}, required rescue medication compared with the aPCC group[30]. Overall, based on the findings from these two trials, a Cochrane Collaboration review reported that there was no conclusive evidence that the efficacy of one product was superior to that of the other[31]. Anecdotal reports describe improved efficacy with combination or sequential use of the two bypassing products. Although *in vitro* thrombin generation data may support this strategy, it should be considered experimental and reserved to hospital treatment when other interventions fail and after appropriate risk-benefit assessment[32]. Indeed, the most serious concern of bypassing treatment remains the risk of thrombotic complications, including myocardial

Table I - Characteristics and regimens of bypassing agents used for treatment of inhibitor patients.

	aPCC (FEIBA)	rFVIIa (NovoSeven)
Origin	Plasma-derived	Recombinant
Recommended regimen(s)	50-100 I.U. kg^{-1} every 8-12 hrs (not to exceed 200 I.U. kg^{-1} d^{-1})	90-120 μg kg^{-1} every 2-3 hrs; single dose 270 μg kg^{-1}
Prophylactic use	Reported in literature (50-100 I.U. kg^{-1} 2-7 × week)	
Licensed (85 I.U. kg^{-1} 3 × week)	Reported in literature (200 μg kg^{-1} weekly - 270 μg kg^{-1} d^{-1})	
Inhibitor anamnesis	Possible	No
Volume	20 mL (500 I.U. or 1,000 I.U.)	1 mL (1 mg)
Association with antifibrinolytic agents	Reported following a single dose; advised against when administering repeated dosing.	Commonly used, even in major surgery
Laboratory monitoring	Not standardised	Not standardised
Thrombotic risk	Yes	Yes

Legend aPCC: activated prothrombin complex; rFVIIa: activated recombinant factor VII; I.U.: international units.

infarction, venous thromboembolism and disseminated intravascular coagulation. This issue is emphasised by the lack of easily available and validated laboratory tools for monitoring treatment and identifying an exaggerated activation of coagulation, although increasing data on global haemostasis assays are being collected[33]. Fortunately, the incidence of these adverse events is very low, occurring in most cases in the presence of other recognised risk factors and/or during prolonged, high-dose treatment. According to a pharmacovigilance assessment including data from published case reports and from the United States of America Food and Drug Administration Medwatch program in the period 1999-2002[34], thrombotic complications resulted significantly more frequent in rFVIIa than aPCC recipients (24.6 *vs* 8.24 per 10^5 infusions, incidence rate ratio 2.98, 95% confidence interval 1.71-5.52). These data have been disputed, taking into account the inclusion of rFVIIa off-label treatments in non-haemophilic patients and the possibility of under-reporting adverse events for an older product like aPCC. Nevertheless, this debate highlights the need for caution regarding indications and dosages of treatment with bypassing agents and further vigilance and data collection in this setting.

The need for avoiding recurrent bleeding and the consequent joint deterioration in children with inhibitors candidate to or during ITI, and for reducing the severity or the frequency of bleeds even in some adolescent or adult patients, led to experience prophylaxis regimens with bypassing agents. Retrospective case reports or series reported improvements of bleeding frequency, patients' physical activity and quality of life with a variety of regimens with both aPCC (50-100 I.U. kg^{-1} from once daily to four times weekly) and rFVIIa (from 200 μg kg^{-1} per week to 270 μg kg^{-1} daily)[13]. As regards rFVIIa, a prospective randomised study showed benefits not statistically different using daily doses of 90 or 270 μg kg^{-1} which, interestingly, were maintained over a 3-month post-prophylaxis follow-up[14]. Recently, a prospective, randomised crossover study comparing 6 months of aPCC prophylaxis (85 U kg^{-1} on 3 days weekly) with 6 months of on-demand therapy (Pro-FEIBA study) reported significant 62% reduction in all bleeding episodes, 61% reduction in haemarthroses, and 72% reduction in target-joint bleeding during prophylaxis[15]. Although patients' responsiveness was quite heterogeneous, based on this study, FEIBA is the only bypassing agent actually registered for prophylaxis in haemophilia patients with inhibitors. If improvement of bleeding frequency is reported in most treated patients, few data are available concerning long-term effects of such regimens on joint outcome. However, the encouraging clinical results led to hypothesize an early start of prophylaxis even in children with inhibitors, with the aim of preventing life-threatening haemorrhages and minimising joint deterioration while awaiting for ITI start[13,35].

On the whole, the management of inhibitor patients with bypassing agents deserves a series of unsolved issues, including 10-20% of bleeds not satisfactorily treated, the variability and, often unpredictability of response, the lack of validated laboratory assay(s) for monitoring of efficacy and safety of treatment. These aspects need continuous clinical vigilance and further concerted research efforts, even in order to identify more cost-effective regimens of treatment. The issue of costs of inhibitor patients, being 3-15 higher than those of non-inhibitor ones[11,36,37], indeed, is even more relevant in the current economic scenario.

By-passing agents in the management of acquired haemophilia with inhibitors

AH is a rare (reported incidence approximately 1.5 per million/year)[38] but often severe bleeding disorder caused by autoantibodies against coagulation factors, in most cases FVIII[39]. AH occurs more frequently in the elderly and in association with several conditions, such as malignancies, autoimmune diseases, postpartum or drug exposure; however, about half of cases remain idiopathic[39]. At variance with congenital haemophilia, in which haemarthroses are the most common bleeding symptoms, in AH haemorrhages involving soft tissues (muscle, skin) are more frequently reported. Prompt recognition and treatment of AH are mandatory, as inadequate management and complications of the disease are associated with high mortality rates[6,39]. The therapeutic approach is aimed at controlling acute bleeds, eradicating the FVIII-autoantibody production and removing, when possible, associated diseases. Present knowledge about this often overlooked, challenging condition has been significantly increased by recent national and international studies, in particular the recently published prospective European ACquired Haemophilia (EACH) 2 Registry[40]. By-passing agents are considered the first-choice treatment of bleeding in AH, being associated with higher response rates than treatment with FVIII concentrates and desmopressin[6,40]. Regimens of treatment are substantially extrapolated by those used in patients with congenital haemophilia and allantibodies[39]. Studies addressing a head-to-head comparison of aPCC and rFVIIa are lacking, however high response rates have been reported for both agents. More data are available for rFVIIa, which was the largely most used first-line agent even in the EACH2 Registry (51% of bleeds *vs* 19% APCC and 18% FVIII concentrate)[40]. Better results are reported when rFVIIa was used as first-line treatment (up to 100%) than as a salvage approach. aPCC provided haemostatic efficacy in

76-100% of treated bleeds, with higher rates in moderate bleeding episodes[39]. Concerns for thromboembolic risk have been raised also in this setting, particularly with respect to the elderly age and concomitant vascular risk factors of the majority of patients. However, the EACH2 Registry showed a low incidence of such adverse events (2.6%), similar in patients receiving both bypassing agents and untreated patients[40].

Recombinant FVIIa in FVII deficiency and Glanzmann's thrombasthenia

Replacement treatment is needed in symptomatic patients with FVII deficiency or for haemostatic coverage of invasive procedures[7]. The most common symptoms are bleeding post-injury and mucosal bleeding, followed by haematoma, haemarthrosis and gastro-intestinal bleeding. Although bleeding phenotype cannot be easily predicted in this setting, spontaneous bleeding usually occurs in patients with residual coagulant FVII activity <10%[41]. Sources of FVII replacement are fresh frozen plasma and FVII concentrates, including plasma-derived products and rFVIIa. The latter was the most used replacement agent both for treatment of bleeding episodes[42] or prevention of bleeding under invasive procedures[43,44] in the recently published prospective Seven Treatment Evaluation Registry (STER). Largely variable regimens of treatment were used in terms of rFVIIa doses and intervals of administration, however a dose range of 15-30 μg kg^{-1} is recommended, every 6-12 hours. In the case of surgery, the analysis from the STER suggested that effective replacement should provide single doses of at least 13 μg kg^{-1} for no less than 3 administrations[44]. In patients with severe and recurrent bleeding (intracranial, gastrointestinal, joint), prophylactic regimens have been proposed, in spite of the short half-life of FVII. The experience collected in the STER show that regimens consisting of at least thrice-weekly rFVIIa administration (total dose 90 μg) provided excellent outcomes[45] without adverse events, confirming the rationale for long-term prophylaxis in FVII deficiency with severe bleeding phenotype.

GT is a rare, autosomal recessive platelet disorder, characterised by a quantitative or qualitative defect of platelet surface α_{IIb}-β_3 integrin (glycoprotein IIb/IIIa complex), leading to the failure of platelets to bind fibrinogen, retract a fibrin clot or aggregate after physiological stimuli[46]. GT patients typically show a mucocutaneous pattern of bleeding, with epistaxis, menorrhagia, gingival haemorrhage, easy bruising and ecchymoses. Gastrointestinal bleeding and haematuria are less common, whereas haemarthroses and deep haematomas only seldom occur. However, most patients (>2/3) require blood and/or platelet transfusions at least once in their life, although bleeding phenotype is dramatically variable, some patients having only minimal bruising, others frequent, severe, potentially fatal haemorrhages[8,46]. Due to the rarity of the disease, there is a general lack of rigorous evidence regarding management of GT patients, being only available information from case series and recommendations of expert panels, often extrapolated from other settings of platelet disorders[8]. If minor bleeding is usually managed with local haemostatic measures and antifibrinolytic agents, in the case of major bleeding, when other approaches are unable to control bleeding, or for prophylaxis in surgery, platelet transfusions are considered the standard treatment. However, many unsolved issues concerning platelet transfusions remain, including poor standardisation of treatment and outcome assessment, the residual risk of blood-borne infections, and immunologic complications, in particular the development of alloantibodies against α_{IIb}-β_3 integrin and/or human leukocyte antigens (HLA), with possible refractoriness to future platelet transfusion[8,46,47]. Moreover, these antibodies may cross placenta to result in harm to the foetus/newborn in pregnant women, causing thrombocytopaenia and/or bleeding[46,48]. These concerns, particularly in young patients and in fertile women, led to experience the use of rFVIIa as an alternative haemostatic agent, in the light of preliminary reports of efficacy in patients with GT or other platelet disorders[49-51]. An International survey collecting 59 patients treated for 108 bleeding episodes and 34 invasive procedures confirmed the efficacy and safety of rFVIIa bolus injections of ≥80 μg kg^{-1} at intervals of ≤2.5 hours, for at least 3 doses, in particular in non-gastrointestinal bleeding and when early administered after bleeding onset[52]. Presently, rFVIIa is licensed in Europe for GT patients with platelet alloimmunisation and history of platelet refractoriness. A 5-yr International prospective registry (GTR, Glanzmann's Thrombasthenia Registry) has been recently terminated and will provide further information concerning the clinical use of rFVIIa in this setting[53].

Quantification of aPCC and rFVIIa demand in Italy

In Italy, data on the utilisation of medicinal products containing aPCC and rFVIIa are collected by the medicinal products traceability at the Italian Ministry of Health[54]. Tables II and III show total (public and private) and total standardised demand for aPCC, expressed in FEIBA Units (F.U.) and per 1,000 population F.U., respectively, in the period 2007-2011, at national and regional level. The aPCC national demand showed an increase of 25% with an absolute value of 17,445,000 F.U. in the last year (Table II). The national standardised demand was about 288 per 1,000 population F.U. (Table III), with an increasing trend (+22%).

Table II - Quantification of total (public and private) demand for products containing activated prothrombin complex concentrate (expressed in FEIBA units) in Italy and Italian regions, from 2007 to 2011.
Source: medicinal product traceability, processed and adapted by the Italian National Blood Centre.

Region	2007	2008	2009	2010	2011
Abruzzo	975,000	1,223,000	-	288,000	1,044,000
Aosta Valley	-	-	-	-	-
AP Bolzano	-	-	-	13,000	14,000
AP Trento	-	-	-	-	-
Apulia	528,000	378,000	502,000	221,000	165,000
Basilicata	-	-	-	-	-
Calabria	152,000	636,000	35,000	-	75,000
Campania	2,572,000	2,267,000	327,000	1,298,000	1,914,000
ER	1,231,000	660,000	-	431,000	872,000
FVG	-	-	-	560,000	854,000
Latium	3,447,000	434,000	2,264,000	5,319,000	6,357,000
Liguria	-	-	-	-	1,129,000
Lombardy	878,000	401,000	452,000	824,000	2,855,000
Marche	85,000	-	-	124,000	404,000
Molise	-	-	-	-	-
Piedmont	379,000	10,000	-	74,000	336,000
Sardinia	-	-	-	-	10,000
Sicily	876,000	389,000	768,000	384,000	183,000
Tuscany	1,326,000	262,000	1,000	80,000	560,000
Umbria	-	-	-	-	40,000
Veneto	637,000	-	12,000	518,000	633,000
Other*	911,000	5,000	176,000	-	-
Italy	13,997,000	6,665,000	4,537,000	10,134,000	17,445,000

Legend -: absence of utilisation; AP: Autonomous Province, ER: Emilia-Romagna; FVG: Friuli-Venezia Giulia; Other*: movements of medicinal products not univocally defined.

Table III - Quantification of total (public and private) standardised demand for products containing activated prothrombin complex concentrate (expressed in per 1,000 population FEIBA units) in Italy and Italian regions, from 2007 to 2011.
Source: medicinal product traceability, processed and adapted by the Italian National Blood Centre.

Region	2007	2008	2009	2010	2011
Abruzzo	744.4	923.7	na	215.1	777.7
Aosta Valley	na	na	na	na	na
AP Bolzano	na	na	na	25.8	27.6
AP Trento	na	na	na	na	na
Apulia	129.7	92.7	123.0	54.1	40.3
Basilicata	na	na	na	na	na
Calabria	76.1	316.8	17.4	na	37.3
Campania	444.2	390.1	56.3	222.8	328.1
ER	291.5	154.4	na	98.1	196.7
FVG	na	na	na	453.8	691.0
Latium	627.5	78.0	402.4	936.1	1.109.7
Liguria	na	na	na	na	698.3
Lombardy	92.0	41.6	46.4	83.9	287.9
Marche	55.3	na	na	79.5	258.1
Molise	na	na	na	na	na
Piedmont	87.1	2.3	na	16.6	75.4
Sardinia	na	na	na	na	6.0
Sicily	174.6	77.3	152.4	76.1	36.2
Tuscany	364.5	71.3	0.3	21.4	149.3
Umbria	na	na	na	na	44.1
Veneto	133.4	na	2.5	105.4	128.2
Other*	na	na	na	na	na
Italy	236.7	111.8	75.6	167.9	287.7

Legend AP: Autonomous Province; ER: Emilia-Romagna; FVG: Friuli-Venezia Giulia; Other*: movements of medicinal products not univocally defined; na: not assessable.

Tables IV and V show both the total and standardised demand, expressed in milligrams (mg) and per 1,000 population mg, respectively, for rFVIIa in the period 2010-2011, at national and regional level. The national rFVIIa demand is constantly increasing: +153% from 2010 to 2011. In 2011, total use has been estimated at 89,170 mg (Table IV) and 1.1 per 1,000 population mg (Table V).

The data collected in this study did not enable to distinguish the indications for the aPCC and rFVIIa requirement, however these figures actually reflect the clinical use of bypassing agents for patients with haemophilia with inhibitors in Italy, and in particular for those with congenital haemophilia and alloantibodies. Indeed, although some patients with AH require intensive and prolonged haemostatic treatment, the rarity of this bleeding disorder (approximately 80 cases per year may be estimated taking into account the total population of Italy) and the limitation of bleeding risk to the time frame of the presence of inhibitors, make the impact of demand for such indication less relevant than that for management of inhibitor patients with congenital haemophilia. More than 300 patients are registered as having a history of inhibitor in Italy[55,56], however, the number of patients with actual presence of inhibitors and requirement for bypassing treatment is lower, excluding transient inhibitors and those successfully eradicated by ITI. The contribution of other clinical indications of rFVIIa is likely to be negligible, taking into account the rarity of FVII deficiency and GT and the low proportion of patients with these bleeding disorders requiring systemic haemostatic treatment[7,8]. Moreover, the clinical use of rFVIIa for off-label indications in patients with major/life-threatening bleeding[57] is presently reserved to anecdotal cases, in the light of insufficient evidence of efficacy and concerns for adverse events[58,59].

The increase in the demand for bypassing agent, in particular for rFVIIa, cannot be explained by an increase of numbers of inhibitor patients. It is documented that the number of newly diagnosed children with severe haemophilia A, the major contributors to newly developed inhibitors, is unchanged between 2008 and 2011 (approximately 22/year)[56]. No evidence of higher impact of factors associated with inhibitor development is reported over the study period and, on the other hand, the Italian registry of ITI treatment, started in 2005, show a tendency to attempt inhibitor eradication not only in children with recent-onset inhibitors, but also in adults with long-standing inhibitors, with similar success rates[60]. Reasons for such increase should be searched in the better awareness of physicians (and patients trained for home treatment) of optimal regimens of treatment with bypassing agents and of the associated benefits in the resolution of bleeding and its consequences on joint status. These objectives are even more important in the management of children

Table IV - Quantification of total (public and private) demand for products containing recombinant activated clotting factor VII concentrate (expressed in milligrams) in Italy and Italian regions, from 2007 to 2011.
Source: medicinal product traceability, processed and adapted by the Italian National Blood Centre.

Region	2007	2008	2009	2010	2011
Abruzzo	442	828	1,192	147	759
Aosta Valley	100	16	36	22	10
AP Bolzano	187	35	54	89	58
AP Trento	62	86	189	194	53
Apulia	1,064	2,861	2,337	6,725	6,301
Basilicata	31	307	24	284	194
Calabria	-	-	2,088	2,045	3,468
Campania	3,858	8,194	7,076	5,453	11,680
ER	3,169	1,343	5,530	6,972	5,950
FVG	6,910	7,006	5,636	8,539	9,946
Latium	913	2,431	2,531	6,209	4,603
Liguria	164	322	203	510	819
Lombardy	7,117	6,510	3,319	6,659	7,331
Marche	341	778	2,293	4,272	4,207
Molise	-?	34	44	84	48
Piedmont	6,857	8,699	8,059	8,416	10,392
Sardinia	-	-	2,447	489	80
Sicily	-	-	3,520	4,562	5,066
Tuscany	739	11,414	14,583	9,016	12,627
Umbria	253	156	441	271	611
Veneto	3,067	4,420	5,346	6,333	4,961
Other*	6	1	-	-	6
Italy	35,281	55,439	66,949	77,291	89,170

Legend -: absence of utilisation; AP: Autonomous Province; ER: Emilia-Romagna; FVG: Friuli-Venezia Giulia; Other*: movements of medicinal products not univocally defined.

Table V - Quantification of total (public and private) standardised demand for products containing recombinant activated clotting factor VII concentrate (expressed in milligrams per 1,000 population) in Italy and Italian regions, from 2007 to 2011. Source: medicinal product traceability, processed and adapted by the Italian National Blood Centre.

Region	2007	2008	2009	2010	2011
Abruzzo	0.3	0.6	0.9	0.1	0.6
Aosta Valley	0.8	0.1	0.3	0.2	0.1
AP Bolzano	0.4	0.1	0.1	0.2	0.1
AP Trento	0.1	0.2	0.4	0.4	0.1
Apulia	0.3	0.7	0.6	1.6	1.5
Basilicata	0.1	0.5	0.0	0.5	0.3
Calabria	na	na	1	1	1.7
Campania	0.7	1.4	1.2	0.9	2
ER	0.8	0.3	1.3	1.6	1.3
FVG	5.7	5.7	4.6	6.9	8
Latium	0.2	0.4	0.4	1.1	0.8
Liguria	0.1	0.2	0.1	0.3	0.5
Lombardy	0.7	0.7	0.3	0.7	0.7
Marche	0.2	0.5	1.5	2.7	2.7
Molise	na	0.1	0.1	0.3	0.2
Piedmont	1.6	2	1.8	1.9	2.3
Sardinia	na	na	1.5	0.3	0.0§
Sicily	na	na	0.7	0.9	1
Tuscany	0.2	3.1	3.9	2.4	3.4
Umbria	0.3	0.2	0.5	0.3	0.7
Veneto	0.6	0.9	1.1	1.3	1
Other*	0.0	0.0	na	na	0.0
Italy	0.6	0.9	1.1	1.3	1.5

Legend AP: Autonomous Province; ER: Emilia-Romagna; FVG: Friuli-Venezia Giulia.
§Values expressed with "0.0" do not identify absence of demand (which is expressed with "-"), but small quantities of consumption that should need too many decimal figures to be clearly inserted into the table. Other*: movements of medicinal products not univocally defined. na: not assessable.

with inhibitors, in whom preserving joint health from the inhibitor-related enhanced morbidity is crucial, in the perspective of inhibitor eradication and restoring of FVIII prophylaxis[35,61]. In this respect, in the light of the encouraging published results[13-15], prophylactic regimens with both bypassing agents are increasingly introduced in th common clinical practice, in particular in children before starting and during ITI, in whom the most used agent is rFVIIa. Therefore, the constant increase in rFVIIa demand is likely to reflect its predominant use in paediatric inhibitor patients, with more intensive regimens of treatment, including prophylaxis started early after inhibitor detection[13,35].

Another reason for the increasing demand for bypassing agents may rely on a higher number of invasive procedures, in particular orthopaedic surgical interventions, in inhibitor patients. Indeed, over the last decade the improved experience in haemostatic treatment with bypassing agents, together with advances in surgical techniques and rehabilitation, made it possible to extend surgical indications in inhibitor patients, previously denied unless essential because of concern about the reliability with which haemostasis could be achieved and maintained in such patients[62]. Therefore, orthopaedic interventions are now considered in order to improve the patients' quality of life significantly. Specific recommendations have been developed for the use of both bypassing agents[63,64], but in most countries, including Italy, a wide experience with rFVIIa has been achieved[65].

As regards regional demand, the heterogeneity of data is not likely to reflect different clinical approaches, but rather the tendency to follow inhibitor patients in a few specialised centres and/or the presence of cases with specific high treatment requirements.

Monitoring clinical demand for a therapeutic agent or treatment should be associated with careful assessments of outcomes, particularly in the long-term perspective. Therefore quantitative analysis should be implemented and carried out together with specific evaluations of indications, follow-up of global clinical results and cost-effectiveness and cost-utility assessment. This is mandatory in a setting like that of bypassing agents and management of inhibitor patients, in which a huge investment of healthcare resources is needed and few data on long-term achievements are available.

Keywords: activated prothrombin complex, activated recombinant factor VII, demand, factor concentrates, utilisation.

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Antonio Coppola received fees as a speaker in educational activities from Bayer Healthcare and Biotest and acted as a member of an advisory board of Bayer Healthcare.

Annaruta Tagliaferri acted as a consultant to Bayer HealthCare and as a member of an advisory board of Novo Nordisk

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Giovanni Di Minno acted as a speaker or a member of a Speakers Bureau for Bayer, Biotest, Boehringer Ingelheim, Grifols, Novo Nordisk, Pfizer and Sanofi-Aventis and as a consultant or ad hoc *speaker/consultant for Bayer, Biotest, Boehringer Ingelheim, CSL Behring, Eli-Lilly, Grifols, Novo Nordisk and Pfizer.*

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References

1) Franchini M, Coppola A, Tagliaferri A, Lippi G. FEIBA versus NovoSeven in hemophilia patients with inhibitors. Semin Thromb Hemost 2013; **39**: DOI 10.1055/s-0033-1354425.
2) Cromwell C, Aledort LM. FEIBA: a prohemostatic agent. Semin Thromb Hemost 2012; **38**: 265-7.
3) Franchini M, Lippi G. Recombinant activated factor VII: mechanisms of action and current indications. Semin Thromb Hemost 2010; **36**: 485-92.
4) Collins PW, Chalmers E, Hart DP, et al. Diagnosis and treatment of factor VIII and IX inhibitors in congenital haemophilia (4th Edition). Br J Haematol 2013; **160**: 153-70.
5) Astermark J, Rocino A, Von Depka M, et al.; EHTSB. Current use of by-passing agents in Europe in the management of acute bleeds in patients with haemophilia and inhibitors. Haemophilia 2007; **13**: 38-45.
6) Huth-Kuhne A, Baudo F, Collins P, et al. International recommendations on the diagnosis and treatment of patients with acquired hemophilia A. Haematologica 2009; **94**: 566-75.
7) Mariani G, Bernardi F. Factor VII deficiency. Semin Thromb Hemost 2009; **35**: 400-6.
8) Di Minno G, Coppola A, Di Minno MND, Poon M-C. Glanzmann's thrombasthenia (defective platelet integrin alphaIIb-beta3): proposals for management between evidence and open issues. Thromb Haemost 2009; **102**: 1157-64.
9) Coppola A, Santoro C, Tagliaferri A, et al. Understanding inhibitor development in haemophilia A: towards clinical prediction and prevention strategies. Haemophila 2010; **16** (Suppl 1): 13-9.
10) Wight J, Paisley S. The epidemiology of inhibitors in haemophilia A: a systematic review. Haemophilia 2003; **9**: 418-35.
11) Gringeri A, Mantovani LG, Scalone L, Mannucci PM; for the COCIS Study Group. Cost of care and quality of life for patients with hemophilia complicated by inhibitors: the COCIS Study. Blood 2003; **102**: 2358-63.
12) Gringeri A, Mannucci PM; for the Italian Association of Haemophilia Centers. Italian guidelines for the diagnosis and treatment of patients with haemophilia and inhibitors. Haemophilia 2005; **11**: 611-9.
13) Carcao M, Lambert T. Prophylaxis in haemophilia with inhibitors: update from international experience. Haemophilia 2012; **16** (Suppl 2): 16-23.
14) Konkle BA, Ebbesen LS, Erhardtsen E, et al. Randomised, prospective clinical trial of recombinant factor VIIa for secondary prophylaxis in hemophilia patients with inhibitors. J Thromb Haemost 2007; **5**: 1904-13.
15) Leissinger C, Gringeri A, Antmen B, et al. Anti-inhibitor coagulant complex prophylaxis in hemophilia with inhibitors. N Engl J Med 2011; **365**: 1684-92.
16) DiMichele D, Hoots WK, Pipe SW, et al. International workshop on immune tolerance induction: consensus recommendations. Haemophilia 2007; **13** (Suppl 1): 1-22
17) Coppola A, Di Minno MN, Santagostino E. Optimizing management of immune tolerance induction in patients with severe haemophilia A and inhibitors: towards evidence-based approaches. Br J Haematol 2010; **150**: 515-28.
18) Batorova A, Morongova A, Tagariello G, et al. Challenges of the management of hemophilia B with inhibitor. Semin Thromb Hemost 2013; **39**: DOI 10.1055/s-0033-1356574.
19) Ehrlich HJ, Enzl MJ, Gomperts ED. Safety of factor VIII inhibitor bypass activity (FEIBA): 10-year compilation of thrombotic adverse events. Haemophilia 2002; **8**: 83-90.
20) Hilgartner MW, Knatterud GL. The use of factor eight inhibitor bypassing activity (FEIBA immuno) product for treatment of bleeding episodes in hemophiliacs with inhibitors. Blood 1983; **61 (1)**: 36-40
21) Negrier C, Goudemand J, Sultan Y, et al. Multicenter retrospective study on the utilization of FEIBA in France in patients with factor VIII and factor IX inhibitors. French FEIBA Study Group. Factor Eight Bypassing Activity. Thromb Haemost 1997; **77**: 1113-9.
22) DiMichele D, Négrier C. A retrospective postlicensure survey of FEIBA efficacy and safety. Haemophilia 2006; **12**: 352-62.
23) Négrier C, Lienhart A, Numerof R, et al. SURgical interventions with FEIBA (SURF): international registry of surgery in haemophilia patients with inhibitory antibodies. Haemophilia 2013; **19**: e143-50.
24) Key NS, Aledort LM, Beardsley D, et al. Home treatment of mild to moderate bleeding episodes using recombinant factor VIIa (Novoseven) in haemophiliacs with inhibitors. Thromb Haemost 1998; **80**: 912-8.
25) Santagostino E, Gringeri A, Mannucci PM. Home treatment with recombinant activated factor VII in patients with factor VIII inhibitors: the advantages of early intervention. Br J Haematol 1999; **104**: 22-6.
26) Kavakli K, Makris M, Zulfikar B, et al. Home treatment of haemarthroses using a single dose regimen of recombinant activated factor VII in patients with haemophilia and inhibitors. A multi-centre, randomised, double-blind, cross-over trial. Thromb Haemost 2006; **95**: 600-5.
27) Santagostino E, Mancuso ME, Rocino A, et al. A prospective randomised trial of high and standard dosages of recombinant factor VIIa for treatment of hemarthroses in hemophiliacs with inhibitors. J Thromb Haemost 2006; **4**: 367-71.
28) Salaj P, Brabec P, Penka M, et al. Effect of rFVIIa dose and time to treatment on patients with haemophilia and inhibitors: analysis of HemoRec registry data from the Czech Republic. Haemophilia 2009; **15**: 752-9.
29) Astermark J, Donfield SM, DiMichele DM, et al; FENOC Study Group. A randomised comparison of bypassing agents in hemophilia complicated by an inhibitor: the FEIBA NovoSeven Comparative (FENOC) Study. Blood 2007; **109**: 546-51.
30) Young G, Shafer FE, Rojas P, Seremetis S. Single 270 microg kg-dose rFVIIa vs. standard 90 microg kg-dose rFVIIa and APCC for home treatment of joint bleeds in haemophilia patients with inhibitors: a randomised comparison. Haemophilia 2008; **14**: 287-94.
31) Iorio A, Matino D, D'Amico R, Makris M. Recombinant Factor VIIa concentrate versus plasma derived concentrates

for the treatment of acute bleeding episodes in people with haemophilia and inhibitors. Cochrane Database Syst Rev 2010; **8**: CD004449.
32) Gringeri A, Fischer K, Karafoulidou A, et al. Sequential combined bypassing therapy is safe and effective in the treatment of unresponsive bleeding in adults and children with haemophilia and inhibitors. Haemophilia 2011; **17(4)**: 630-5.
33) Hoffman M, Dargaud Y. Mechanisms and monitoring of bypassing agent therapy. J Thromb Haemost 2012; **10**: 1478-85.
34) Aledort LM. Comparative thrombotic event incidence after infusion of recombinant FVIIa versus FVIII inhibitor bypass activity. J Thromb Haemost 2004; **2**: 1700-8.
35) Jiménez-Yuste V, Alvarez MT, Martín-Salces M, et al. Prophylaxis in 10 patients with severe haemophilia A and inhibitor: different approaches for different clinical situations. Haemophilia 2009; **15**: 203-9.
36) Di Minno MN, Di Minno G, Di Capua M, et al. Cost of care of haemophilia with inhibitors. Haemophilia 2010; **16(1)**: e190-201.
37) Hay JW, Zhou ZY. Economical comparison of APCC vs. rFVIIa for mild-to-moderate bleeding episodes in haemophilia patients with inhibitors. Haemophilia 2011; **17**: e969-74.
38) Collins P, Hirsch S, Baglin TP, et al. Acquired haemophilia A in the United Kingdom: a 2-year national surveillance study by the United Kingdom Haemophilia Centre Doctors' Organisation. Blood 2007; **109**: 1870-7.
39) Coppola A, Favaloro EJ, Tufano A, et al. Acquired inhibitors of coagulation factors: part I-acquired hemophilia A. Semin Thromb Hemost 2012; **38**: 433-46.
40) Baudo F, Collins P, Huth-Kühne A, et al. Management of bleeding in acquired hemophilia A: results from the European Acquired Haemophilia (EACH2) Registry.Blood. 2012; **120**: 39-46.
41) Peyvandi F, Di Michele D, Bolton-Maggs PH, et al. Classification of rare bleeding disorders (RBDs) based on the association between coagulant factor activity and clinical bleeding severity. J Thromb Haemost. 2012; **10**: 1938-43.
42) Mariani G, Napolitano M, Dolce A, et al. Replacement therapy for bleeding episodes in factor VII deficiency. A prospective evaluation. Thromb Haemost 2013; **109**: 238-47.
43) Mariani G, Dolce A, Napolitano M, et al. Invasive procedures and minor surgery in FVII deficiency. Haemophilia 2012; **18**: e63-5.
44) Mariani G, Dolce A, Batorova A, et al. Recombinant, activated factor VII for surgery in factor VII deficiency: a prospective evaluation - the surgical STER. Br J Haematol 2011; **152**: 340-6.
45) Napolitano M, Giansily-Blaizot M, Dolce A, et al. Prophylaxis in congenital factor VII deficiency: indications, efficacy and safety. Results from the Seven Treatment Evaluation Registry (STER). Haematologica 2013; **98**: 538-44.
46) George JN, Caen JP, Nurden AT. Glanzamann's thrombasthenia: the spectrum of clinical disease. Blood 1990; **75**: 1383-95.
47) Santoro C, Rago A, Biondo F, et al. Prevalence of allo-immunization anti-HLA and anti-integrin alphaIIbbeta3 in Glanzmann Thromboasthenia patients. Haemophilia 2010; **16(5)**: 805-12.
48) Léticée N, Kaplan C, Lémery D. Pregnancy in mother with Glanzmann's thrombasthenia and isoantibody against GPIIb-IIIa: is there a foetal risk? Eur J Obst Gynecol Reprod Biol 2005; **121**: 139-42.
49) Tengborn L, Peturson B. A patient with Glanzmann's thrombasthenia and epistaxis successfully treated with recombinant factor VIIa. Thromb Haemost 1996; **75**: 981-2.
50) Poon M-C, Demers C, Jobin F, Wu JW. Recombinant factor VIIa is effective for bleeding and surgery in patients with Glanzmann thrombasthenia. Blood 1999; **94**: 3951-3.
51) Almeida AM, Khair K, Hann I, Liesner R. The use of recombinant factor VIIa in children with inherited platelet function disorders. Br J Haematol 2003; **121**: 477-81.
52) Poon M-C, d'Oiron R, Von Depka M, et al. Prophylactic and therapeutic recombinant factor VIIa administration to patients with Glanzmann's thrombasthenia: results of an international survey. J Thromb Haemost 2004; **2**: 1096-103.
53) Poon M-C, Zotz R, Di Minno G, et al. Glanzmann's thrombasthenia treatment: a prospective registry on the use of recombinant human activated Factor VII and other hemostatic agents. Semin Hematol 2006; **43** (Suppl 1): S33-6.
54) Lanzoni M, Biffoli C, Candura F, et al. Plasma-derived medicinal products in Italy: information sources and flows. Blood Transfus 2013; **11** (Suppl 4): s13-7.
55) Iorio A, Oliovecchio E, Morfini M, Mannucci PM; Association of Italian Hemophilia Centres Directors. Italian Registry of Haemophilia and Allied Disorders. Objectives, methodology and data analysis. Haemophilia. 2008 ; **14 (3)**: 444-53.
56) Abbonizio F, Gianpaolo A, Arcieri R, et al. *Registro Nazionale delle Coagulopatie Congenite. Rapporto 2011*. Roma: Istituto Superiore di Sanità; 2012. (Rapporti ISTISAN 12/55).
57) Levi M, Peters M, Büller HR. Efficacy and safety of recombinant factor VIIa for treatment of severe bleeding: a systematic review. Crit Care Med 2005; **33**: 883-90.
58) Mannucci PM, Levi M. Prevention and treatment of major blood loss. N Engl J Med. 2007; **356**: 2301-11.
59) Levi M, Levy JH, Andersen HF, Truloff D. Safety of recombinant activated factor VII in randomised clinical trials. N Engl J Med. 2010; **363**: 1791-800.
60) Coppola A, Margaglione M, Santagostino E, et al. Factor VIII gene (F8) mutations as predictors of outcome in immune tolerance induction of hemophilia A patients with high-responding inhibitors. J Thromb Haemost 2009; **7**: 1809-15.
61) Santagostino E, Morfini M, Auerswald GK, et al. Paediatric haemophilia with inhibitors: existing management options, treatment gaps and unmet needs. Haemophilia. 2009; **15**: 983-9.
62) Teitel JM, Carcao M, Lillicrap D, et al. Orthopaedic surgery in haemophilia patients with inhibitors: a practical guide to haemostatic, surgical and rehabilitative care. Haemophilia 2009; **15**: 227-39.
63) Rangarajan S, Austin S, Goddard NJ, et al. Consensus recommendations for the use of FEIBA® in haemophilia A patients with inhibitors undergoing elective orthopaedic and non-orthopaedic surgery. Haemophilia 2013; **19**: 294-303.
64) Giangrande PL, Wilde JT, Madan B, et al. Consensus protocol for the use of recombinant activated factor VII [eptacog alfa (activated); NovoSeven] in elective orthopaedic surgery in haemophilic patients with inhibitors. Haemophilia 2009; **15**: 501-8.
65) Valentino LA, Cooper DL, Goldstein B. Surgical experience with rFVIIa (NovoSeven) in congenital haemophilia A and B patients with inhibitors to factors VIII or IX. Haemophilia 2011; **17**: 579-89.

Correspondence: Antonio Coppola
Regional Reference Centre for Coagulation Disorders
Federico II University Hospital
Via S. Pansini 5
80131 Naples, Italy
e-mail: antocopp@unina.it