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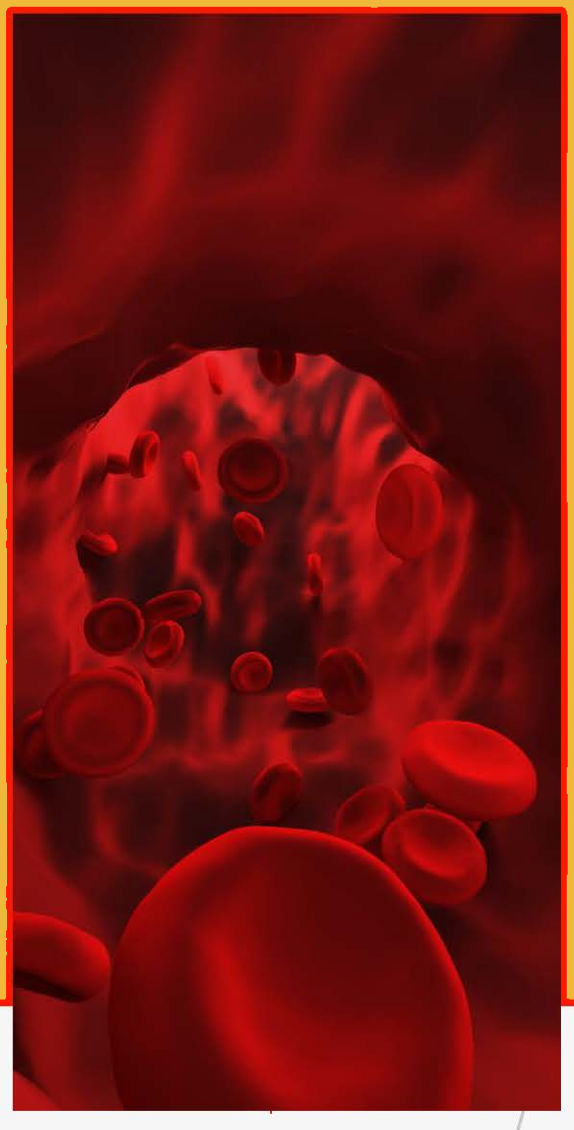

OJHM

Editor: G. SOTTILOTTA

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Contents

Aims and scope

ONLINE JOURNAL OF HEMATOLOGY AND MEDICINE (OJHM) is an interdisciplinary open access online journal focusing primarily on blood diseases. The journal publishes original contributions in non-malignant and malignant hematological diseases. It also covers all the areas related to the hematological field that takes care of diagnosis and treatment of blood disease. Particular editorial interest is addressed to: Inherited and Acquired Clotting Disorders, Antiphospholipid Syndrome, Clinical Management of Bleeding Diseases, Coagulopathies, Hemophilia, Platelets Disorders, Thrombotic Disorders. Manuscripts should be presented in the form of original articles, editorials, reviews, short communications, or cases report, all submissions are rigorously peer reviewed.

All manuscripts submitted to OJHM must be previously unpublished and may not be considered for publication elsewhere at any time during OJHM's review period.

Andrea Buzzi
President of the
Paracelso Foundation

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Letter to the Editor

From patient viewpoint: a perspective on new therapeutic options

What a 60-year-old "guy" with hemophilia today possibly ask for, after having survived a decade without any treatment, and then going through the gloomy years of plasma derivatives tainted with deadly blood-borne viruses like HIV, HBV and HCV, the most appalling drug-induced catastrophe of modern medicine?

After the marketing of recombinant products in the mid '90s, the next 20 years were marked by 2nd and 3rd generation rFVIII and rIX with little, if any, perceived improvement by patients. In the last few years new significantly innovative drugs have been developed, offering an increased efficacy in terms of half-life, which means a higher protection against bleedings and/or less frequent injections. The onset of non-replacement therapy that can be administered subcutaneously has been warmly welcomed by patients. Meanwhile, the ever-receding gene therapy, something we have been hearing about since the '90s, has made great steps forward, some of them no longer in company pipelines but ready to start the registration process, even if its therapeutic scope so far is not curing hemophilia for good but providing a temporary mitigation, and many issues are still open (long term safety, possibility to repeat it, among others).

We are undeniably facing a change of paradigm, requiring and fostering adjustments by both patients and physicians. The most important indicator of the efficacy of hemostatic therapy is the frequency of bleeding, state WFH Guidelines for the Management of Hemophilia. Though FVIII/IX levels have a direct impact on clinical response and can be easily gauged, providing an insight on treatment effectiveness, it's by now well known that microbleeds, that is bleedings that are not apparent, can actually occur, impacting joint health in the long run. While with replacement therapy FVIII/IX levels can be considered a good efficacy metrics, there is so far no direct lab test showing how well non-replacement therapy is working. Here more than ever, we must rely on clinical response. Needless to say, from a patient perspective subcutaneous vs intravenous injection is much easier, and more so, if infusion frequency is once a week instead of 2/3 times a week. It's generally agreed that the choice of treatment should be shared with patients, who in Italy are required to sign an ad hoc informed consent. Given the picture, patient involvement in the decision making process is paramount. After considering the patient's lifestyle, age, and general conditions, including musculoskeletal and vein access, provided no clinical issue advises against non-replacement therapy, what else can guide drug choice if not the patient's preference? This way, a major pharmaceutical innovation is likely to make the difference in the relationship between physician and patient, giving the latter a greater edge in a choice which is now less technically-driven than it used to be. We are living a time of significant advance, the most relevant of which, non-replacement therapy and gene therapy, can probably be seen as a bridge between traditional treatments and a new era where a cure for hemophilia is finally looming. Meanwhile, the above mentioned 60 year-old patient can weigh up the pros and cons of different innovative therapeutic options, including gene therapy, a choice far less predictable than it was only 10 years ago. Which is, in itself, a good sign of the huge progress that has been made.

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Short Report

Usefulness of arthroscopic debridement in patients with chronic severe hemophilic arthropathy of the knee

Introduction:

Hemophilia is a coagulation disorder that causes frequent joint bleeding, the knee being the most affected joint, leading to articular cartilage destruction and functional disability. In young patients with advanced arthropathy (Arnold-Hilgarner III-IV) arthroscopic debridement is an important and valuable treatment in patients who are not candidates for total knee arthroplasty; in this procedure the removal of meniscal fragments, hypertrophic synovium and intercondylar notch remodelling can improve mobility, gait mechanics, and may decrease pain and the number of joint bleedings due to mechanical causes, achieving an improvement within 2 to 5 years.

Objective:

To demonstrate the benefits of arthroscopic debridement, which lead to the improvement of the function, quality of life and to the postponement of the need for a total knee arthroplasty at early age.

Methods:

We studied 20 patients with hemophilia A and B, between the age 20 to 30 years with severe hemophilic knee arthropathy (grade IV) who complained of painful hemarthrosis and on whom arthroscopic debridement was performed.

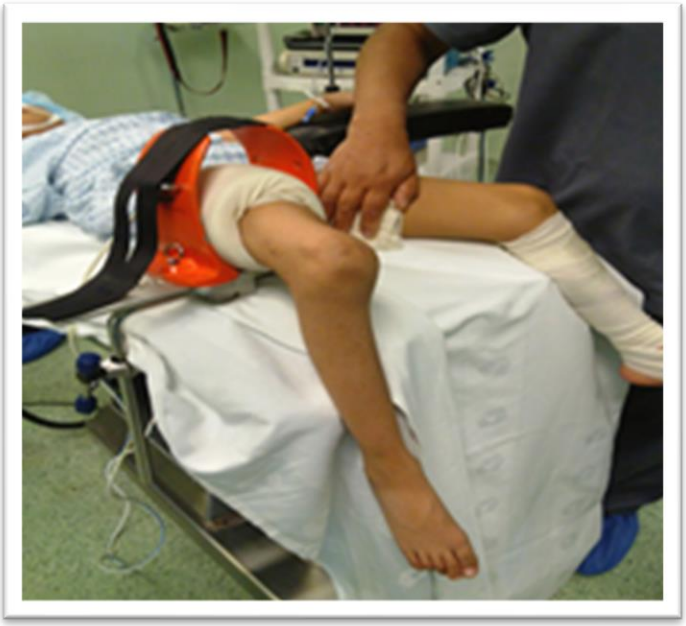

Figure 1: Preparation of a patient with severe hemophilic arthropathy

Results:

12 male patients with severe hemophilia A (one of whom underwent bilateral knee arthroscopy), 2 patients with moderate hemophilia A and 1 with severe hemophilia B, (19-26 years old, average 20.4) were treated with arthroscopic debridement; 3 of them had type C hepatitis and one had inhibitor. Of these 6 received surgery on their right knee, 5 on left knee and 1 on both knees. All of them were treated with previous administration of factor concentrates under supervision of a hematologist, and successively total arthroscopic synovectomy, meniscal remodelling, osteophyte resection, thermal chondroplasty and in 5 cases lateral patellar retinaculum ablation was performed. In all cases the deficit factor concentrate was continued for 3 weeks after surgery; all patients received musculoskeletal rehabilitation before and after surgical procedure, aiming for a better articular mobility range and muscular strength. All patients manifested pain improvement and a wider range of movement.

Conclusions:

The Day Surgery arthroscopic debridement was followed up by a team composed of an orthopaedic surgeon, a hematologist and a physiotherapist, and resulted in an improvement of the painful bleeding joint and the postponement of the need for a total knee arthroplasty by a 5 to 8 year period.

Figure 2: Arthroscopic debridement of the knee in a patient with advanced hemophilic arthropaty

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Letter to the Editor

rFVIII single-chain in an Italian population of hemophilia A patients: the Veneto experience

Dear Editor,
the replacement therapy with clotting factor concentrates is considered the treatment of choice for patients with hemophilia (PWH), both concentrates of plasma origin and those recombinant are in fact considered safe and effective in preventing or treating bleeding.
Prophylaxis is the gold standard of therapies, especially in patients with severe or severe-moderate hemophilia, but in some cases the compliance of patients is reduced due to the need of frequent infusions (1).
In recent years, in addition to new subcutaneous drugs, such as emicizumab (2), which are bringing an epochal breakthrough to the treatment of PWH, several new standard half-life (SHL) or extended half-life (EHL) concentrates have been marketed (3). These drugs often associated with a tailored treatment, based on the pharmacokinetic profile of each patient, as also recently suggested by the latest guidelines of the World Foundation of Hemophilia (1), have improved the compliance of PWH to therapy, and, in many cases, reduced the annual bleeding rate (ABR) and improved their quality of life (QoL). Thanks to these innovative products, even some severe adult patients, always reluctant to long-term therapies, have accepted to start a prophylactic treatment.
Lonoctocog-alfa (Afstyla®), the first and only developed recombinant FVIII (rFVIII) single chain is one of these new drugs. rVIII-SingleChain is a truncated B-domain rFVIII, which has a high affinity for the von Willebrand factor (vWF) and a high stability (4). These two characteristics of the drug have shown a markedly improved pharmacokinetic profile, when compared with octocog-alfa (5). The protective role of vWF has in fact made it possible to reach a plasma half-life of 14.2 ± 3.7 hours, comparable to that of EHL (6), without resorting to molecular modifications as occurs with glyco-pegylation (PEG) or fusion with the antibody fragments (FC). Here we report our experience with rFVIII single-chain in a population of hemophilia A patients, followed for one year and compared with their previous treatment with octocog-alfa. All data were collected one year retrospectively and one year prospectively in four different Hemophilia Centers (Padova, Vicenza, Castelfranco Veneto and Verona) all belonging to the same Italian region (Veneto). The observation began on the day of the switch to Afstyla®. Twenty-one previously treated patients (PTPs), 10-59 years-old were switched to lonoctocog-alfa. 81% had severe hemophilia A, 5% moderate, while three (14%) were mild subjects. 72.6% were adults (≥14 years). Mean weight was 74.5 kg (range 26-128), with a mean BMI of 25 (range 15.9 – 41.8). The blood group was available only for 11/21 patients, seven of them had group 0. vWF:Ag was reported in 20/21 patients, mean 98.6% (range 55-201). Enrolled patients were 61.9% who previously had been on prophylaxis with octocog-alfa (2nd generation), while the remaining eight were treated only on-demand, among these 50% were severe adult patients. Five PTPs on demand with octocog-alfa were subsequently put on prophylaxis with rFVIII single-chain, three of them were young mild subjects who practiced intense

sporting activity. Overall, the mean of total, joint and spontaneous ABR were respectively decreased after the switch to 27.5%, 34.7% and 62.2%, while the weekly median number of infusions remained unchanged, 2 (range 1-3); as did the median dose infused, 2000 IU (range 1000-4000). The detailed comparison of the ABRs (total, joint and spontaneous) between the two different treatments in each patient is shown in Table 1.

ID	Octocog-alpha				rFVIII single-chain			
	Regimen	AtBR	AjBR	AsBR	Regimen	AtBR	AjBR	AsBR
Pt01	PRO	3	3	0	PRO	1	0	1
Pt02	PRO	3	3	3	PRO	2	1	1
Pt03	OD	3	1	3	OD	9	6	3
Pt04	PRO	0	0	0	PRO	0	0	0
Pt05	OD	2	2	2	OD	1	0	1
Pt06	OD	4	2	3	OD	2	2	0
Pt07	PRO	0	0	0	PRO	0	0	0
Pt08	PRO	0	0	0	PRO	0	0	0
Pt09	OD	0	0	0	PRO	0	0	0
Pt10	OD	6	2	0	PRO	1	1	0
Pt11	PRO	1	0	0	PRO	0	0	0
Pt12	PRO	0	0	0	PRO	0	0	0
Pt13	PRO	0	0	0	PRO	0	0	0
Pt14	PRO	0	0	0	PRO	1	1	0
Pt15	PRO	0	0	0	PRO	1	0	1
Pt16	PRO	0	0	0	PRO	0	0	0
Pt17	OD	4	1	3	PRO	1	0	0
Pt18	OD	1	1	1	PRO	0	0	0
Pt19	PRO	5	3	2	PRO	2	2	0
Pt10	PRO	4	2	2	PRO	0	0	0
Pt21	OD	0	0	0	PRO	5	0	0
Mean		1.71	0.95	0.90		1.24	0.62	0.34

Table 1. Overall comparison of total ABR (AtBR), joint ABR (AjBR) and spontaneous ABR (AsBR) between the two different one-year treatments for each enrolled patient. PRO: prophylaxis; OD: on-demand

In addition to a complete analysis of the data obtained from the comparison between the two regimens, a head-to-head comparison of the 13 prophylaxis performed first with octocog-alfa and then with Afstyla® was evaluated. The results are reported in table 2. Also in this case, the overall mean bleeding decrease in total, joint and spontaneous ABR reaching respectively a reduction of 56.1%, 63.5% and 57.4%, while the dose and the number of infusions remained substantially unchanged. The increase, not statistically significant ($p=0.84$) in the estimated annual consumption of lonoctocog-alfa compared to the previous coagulation factor concentrate (363,160 vs 324,920 IU/year) was due to the physiological weight gain of the younger patients treated in prophylaxis who therefore required a dose increase. No differences were found in terms of number of infusions, dosage and ABR among patients with different levels of plasma vWF:Ag. In the Veneto region the cost of Afstyla® was established at 0.509 euro/IU the same as octocog-alfa, this allowed to maintain a similar expenditure despite the physiological annual increase of consumed units. Prophylaxis is the gold standard of care in patients with severe or moderate-severe hemophilia, but the frequent infusions are often the cause of a reduced compliance (7), therefore even today some adult patients prefer a treatment on demand despite the high number of bleedings and the worsening of their hemophiliac arthropathy. A turning point has been achieved in recent years by the arrival of new drugs which, by increasing the efficacy profile and reducing the number of infusions necessary to obtain it, have been well received by patients who in some cases have even accepted to undertake a prophylaxis, previously always rejected. Afstyla®, the only rFVIII single-chain, is one of these new drugs. Its pharmacokinetic profile was proven similar to that of different EHL (6), with a higher affinity to vWF:Ag and without any molecule modification (5).

	Prophylaxis (N=13) octocog-alpha			Prophylaxis (N=13) rFVIII Single-Chain		
	Dose single infusion (IU/kg)	Estimated annual consumption (IU/kg)		Dose single infusion (IU/kg)	Estimated annual consumption (IU/kg)	
Min	15,6	812,5		15,6	1.425,8	
Max	38,5	5.032,3		44,4	5.032,3	
Mean	27,5	3.249,2		31,6	3.631,6	
	ABR	AjBR	AsBR	ABR	AjBR	AsBR
Min	0	0	0	0	0	0
Max	5	3	3	2	2	1
Mean	1,23	0,85	0,54	0,54	0,31	0,23

Table 2. Comparison head-to-head between 13 prophylaxis with octocog-alpha and lonoctocg-alpha. ABR: annual bleeding rate; AjBR: annual joint bleeding rate; AsBR: annual spontaneous bleeding rate.

Also in our case, this new drug was well accepted by the patients, two severe adults also chose to do prophylactic regimen. In recent years there has been much discussion on which trough level to maintain to ensure the best protection for the patient, but there is no single answer, it depends on the lifestyle, the hemorrhagic phenotype and the personal characteristics of each individual subject. It is therefore important to establish a tailored treatment regardless of the severity of the disease, using the help of pharmacokinetics, as suggested by the latest guidelines of the WFH (1). Intense sporting activity is one of the reasons why it is necessary to maintain a high trough level (8), even in mild subjects. In our case, in fact, three young mild patients were put on prophylaxis with lonoctocog-alfa precisely to allow them to safely practice soccer.

In our study, the overall mean annual bleeding rate was reduced after switching to rFVIII single-chain in the patients who were previously on prophylaxis with octocog-alfa, maintaining a mean of two infusions per week. The expected annual mean consumption calculated for the mean weight of our patients (74.5kg) was lower (269,190IU) than that reported by Simpson et al. (9), calculated for an adult patient weighing 70 kg (322,140 IU) or than that of the other two EHL drugs compared in their study. The increase in annual IU consumed with Afstyla® compared to those with octocog-alfa depended only on the physiological weight gain of the young patients on prophylaxis. Since in our region the cost of the single unit of lonoctocog-alfa is identical to that of octocog-alfa, the costs have also remained similar.

In conclusion, we believe that Afstyla, given its pharmacokinetic characteristics and the peculiar construction of its molecule, which makes it similar to the different EHLs available to clinicians, can be a valid alternative and a first choice in patients in whom we want to improve the prophylactic efficacy of replacement therapy and their adherence to treatment.

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Conflict of Interest
All authors declare no conflicts of interest.

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Brief Communication

The SHOT Project: Study Design

Introduction:

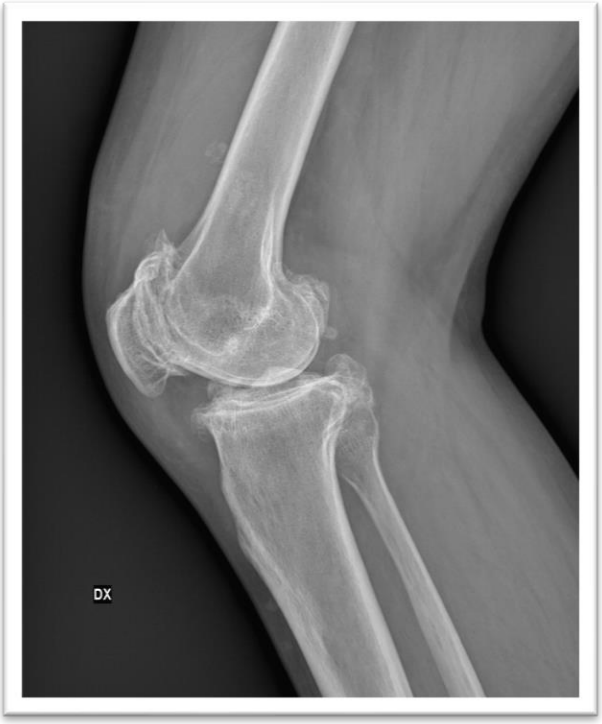
Hemophilia has been associated with low bone mineral density (1,2). In the past years several studies have evidenced increased incidence of osteopenia or osteoporosis in patients with hemophilia A and B (3-5): there are many factors that determine a low peak bone mass during adolescence and then, osteoporosis in adulthood. The SHOT (Severe Hemophilia and Osteoporosis Treatment) project will evaluate the muscle-skeletal health status of the patients of the Hemophilia Centre of Reggio Calabria (Italy) by instrumental measurements of the bone densitometry, blood collections and periodic physiotherapic evaluations. The purpose is the creation of pharmacological treatment protocols associated to specific programs of physical rehabilitation in the young as well in the elderly.

Objective:

The objectives of the SHOT are: evaluate the incidence of osteoporosis in a wide age range of patients with hemophilia, treat pharmacologically those with low bone density with bisphosphonates, coupled with integration of calcium and vitamin D when necessary, and start appropriate rehabilitation programs for prevention of bone loss and fractures for at-risk patients. Other aim will be the improvement of the joint status and the quality of life of patients with haemophilia and osteoporosis, acting at the same time in terms of pharmacological and physiotherapic treatment.

Methods:

We enrolled five patients with severe A hemophilia. Age will undergo to six-month hematologic and physiatric evaluations carried out by expert physiatrist and hematologist. Visits will also include score evaluation based on the joint international scales of measurement, as well as an assessment of quality of life using specific questionnaires. Patients will perform periodic venipunctures in order to investigate the following values: fVIII or fIX activity levels and inhibitor titres, creatinine, total calcium, albumin, phosphorus, alkaline phosphatase, transaminases, bilirubin and prothrombin time, and screening for hepatitis B virus (HBV), HCV and HIV. The examination will be completed by instrumental measurement of bone density.



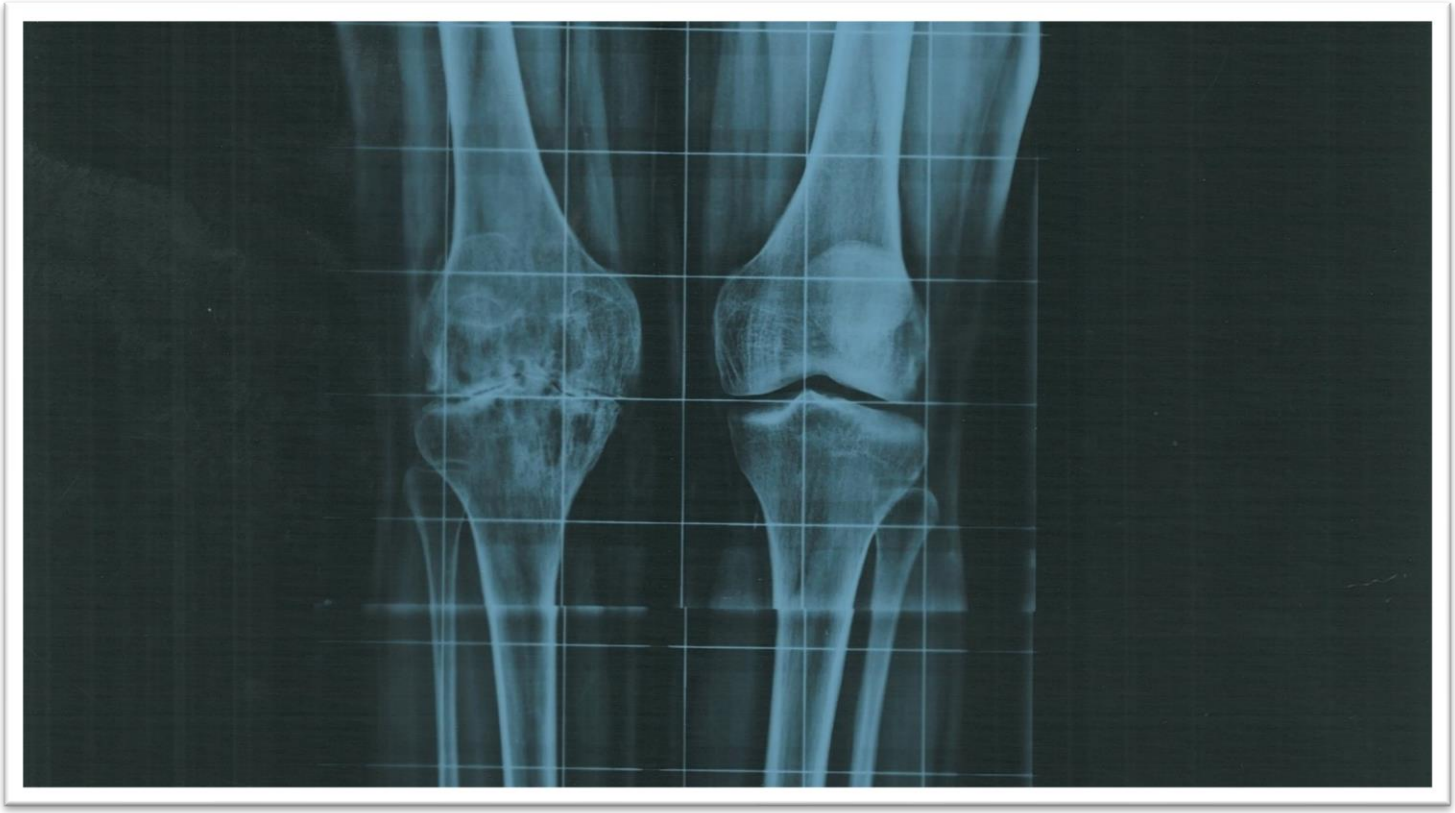
Results:

The results of blood tests and instrumental exams (bone mineral density test) after the assessment of the health status, will be used to establish a protocol drug therapy based on

bisphosphonates, calcium and vitamin D and also an individual program of physical rehabilitation tailored to the obtained results as well patients' clinical characteristic. At the end of the project the results will be also analyzed in order to evaluate the statistical significance.

Discussion:

The expected results from the realization of the SHORT project could be confirm that osteoporosis can be considered as a complication of hemophilia, and also the use of specific combination of drugs of new generation can limit damages from low bone density. This treatment both to an adequate program of physical rehabilitation, may limit the occurrence of arthritic complications, or orthopedic surgery, with resulting in lower costs for the NHS, but also in term of significant improvement in quality of life of patients and their families



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Original Manuscript

Efficacy and safety of prothrombin complex concentrate and Vitamin K in a cohort of 76 patients with anticoagulation-related acute intracranial hemorrhage: clinical features and outcomes at three months

Abstract.
Central nervous bleeding emergencies are the most serious complications of Oral Anticoagulant Therapy (OAT), with an incidence of 1% per patient-year. From January 2004 through January 2010, we observed 79 episodes of anticoagulation-related acute intracranial hemorrhages (AIH) in a cohort of 76 consecutive patients reporting to our emergency department. All patients were treated with a systematic approach: single bolus of 25-30 IU per Kilogram of Prothrombin Complex Concentrate (PCC) and intravenous administration of 10 mg of vitamin K1 within one hour after baseline CT scan of the head. All the patients simultaneously received urgent neurosurgical evaluation. Patients' history, clinical and serological data and ongoing therapy were recorded and analyzed. Functional outcomes at 90 days were assessed with the modified Rankin Scale. Median age of our cohort was 77,6 years (range 38-90) with a male-female ratio of 1,32; indications for OAT were: atrial fibrillation in 65 (82%), heart valve prostheses in 10 (13%), other indications in 4 cases (5%). 18 patients (29%) needed emergency neurosurgical intervention; 35 (44%) patients reported a recent trauma. Acute reversal of OAT (INR<1,5) was obtained in 90% of cases within 30 minutes after therapy administration. 8 subjects had non-fatal thrombotic events, (7 pulmonary embolisms and 1 ischemic stroke). Mortality rate at 90 days was 40%. Although hypertension is a well-known risk factor for intracranial hemorrhage, surprisingly in our cohort a previous history of hypertension was associated with a favorable outcome (p<0,002), possibly due to better control of blood pressure during acute bleeding. Of 48 patients alive after three months, 35 (73%) showed a Rankin score ≥4 at diagnosis, 24 (50%) at discharge and only 13 (27%) at three months. These data reveal the possibility of a remarkable margin of recovery improvement and make rapid treatment mandatory.

Introduction

Central nervous bleeding emergencies are the most serious complications of Oral Anticoagulant Therapy (OAT) with an incidence of 1% per patient-year (1). Anticoagulation-related acute intracranial hemorrhage (AIH) accounts for 20% of all intracranial hemorrhages. Aging of population and increased incidence of atrial fibrillation results in a dramatic increase of the use of antivitamin k antagonists (AVKs) and consequent increase of their more severe complications, particularly in people over 80 years old (2,3). Anticoagulation with AVKs increases 2 to 5 times the risk of intracranial hemorrhage (ICH), with a direct correlation to the intensity of anticoagulation; nevertheless, most AIH occur at anticoagulation intensities within the conventional therapeutic range (i.e., INRs of 2.0-3.5). (4).

AIH recognize the same pathogenesis of spontaneous intracranial hemorrhages (SIH). Magnetic resonance studies demonstrate that cerebral microhemorrhages occur even in healthy individuals. Aging of population, cerebral amyloid angiopathy, hypertension are common causes of both SIH and AIH; in fact, localizations of hematomas are similar in SIH and AIH. So, one may argue that probably OAT simply increases the incidence of intracranial hemorrhage. Nevertheless, AIH are characterized by larger initial hematoma extension when INR>3, (5) and by wider hematoma expansion, as bleeding can persist up to 24 hours after onset (6). These features confer a higher mortality in comparison with SIH and open a temporal window for therapeutic interventions. The degree of INR prolongation at the time of AIH seems to be predictive of progressive hematoma enlargement after admission, functional outcome and mortality, although some authors have reported no correlation. The 1-day mortality of patients with OAT-ICH has been reported to be 33% compared to 16% for SIHs. Large hematoma volume (>50 mL), intraventricular leaking, and shift of midline structures are associated with poorer outcome in SIH. AIH are characterized by larger initial volumes, higher frequency of hematoma enlargement and higher incidence of progressive neurological deterioration in the first 24-48 hours.

Number of patients	76
Number of intracranial hemorrhages	79
Median Age (range)	77.6; (38-90)
Male/female ratio:	1.32
Indication for anticoagulant therapy	
• Atrial fibrillation (%)	65/79 (82%)
• Venous thromboembolism (%)	4/79 (5%)
• Mechanical heart valves	10/79 (13%)
Supratherapeutic INR (>3,5)	16/79 (20%)
Therapeutic INR (2-3,5)	56/79 (71%)
Subtherapeutic INR (<2)	7/79 (9%)
Type of intracranial hemorrage	
• Subdural hematoma (%)	36/79 (46%)
• Lobar hemorrhage	27/79 (34%)
• Deep hematoma	12/79 (15%)
• Subarachnoidal hemorrage	3/79 (4%)
• Cerebellar hemorrage	1/79 (1%)
• Intraventricular inundation	15/79 (19%)
• Spontaneous hemorrage	43/79 (54%)
History of fall or trauma within 15 days before bleeding	35/79 (44%)
Neurosurgical operations	18/79 (23%)
Thromboembolic complications	8/79 (10%)
Hemorrage-related deaths	32/79 (40,5%)

Table 1: Patients characteristics

In spite of the importance of this problem, there are no randomized trials assessing clinical outcomes treatment of AIH (7). The aim of this single center investigator-driven observational retrospective study is to evaluate efficacy and safety of a prothrombin complex concentrate (PCC) on reverting the anticoagulant effect of vitamin K antagonists, and to describe the long-term outcome of AIH at three months' follow up.

Materials and method

From January 2004 through January 2010, we observed 79 consecutive episodes of anticoagulation-related acute intracranial hemorrhage (AIH) in a cohort of 76 consecutive patients reporting to the Emergency Department of the non academic public hospital of Ivrea, Piedmont, Italy (catchment area: 300,000 inhabitants). Data were collected retrospectively from the following sources: patient electronic medical records, emergency department reports, neurology and rehabilitation discharge charts, CT and MRI scans report series, specialized database software for anticoagulation management. Table 1 describes the characteristics of our cohort of patients.

The indications for anticoagulant therapy were: atrial fibrillation in 65 (82%) patients, venous thromboembolism in 4 patients and heart valve prostheses in 10 (13%). All patients were treated with a systematic approach: OAT interruption, single bolus of 25-30 IU per Kilogram of Prothrombin Complex Concentrate (PCC) (Uman Complex, Kedrion, Castelvecchio Pascoli, Italy) and intravenous administration of 10 mg of vitamin K1 (Konakion, Roche, Milano, Italy) diluted in 100 ml of physiological solution within 30 minutes after baseline CT scan of the head.

All patients received urgent neurosurgical evaluation (Table 2). Patients with neurosurgical indication were transferred from Ivrea Hospital to the neurosurgical Dept of a regional Hospital in Turin at a distance of 50 km after receiving treatment with aPCC + vit. K. All but eight patients were followed up at our anticoagulation clinics for at least three months. We analyzed the following variables in order to evaluate fatality rate: age, sex, indication for OAT, INR, PTT, fibrinogen at admission and after PCC bolus, site of intracranial bleeding, prior neurosurgery, prior history of diabetes, hypertension and chronic cerebral vasculopathy, platelets count, hemoglobin and hematocrit, serum cholesterol level. We also traced INR values in the previous three months before intracranial hemorrhage, and investigated for traumatic events and drug interactions (we regarded as significant any association of oral anticoagulants with anti-inflammatory drugs and antiplatelet medications). Furthermore, although there are no definitive conclusions about hemorrhagic risk of selective serotonin reuptake inhibitors (SSRI), (8) we recorded concomitant administration of such antidepressant medications.

Step 1	Oral anticoagulant therapy withdrawal
Step 2	Single bolus of 25-30 IU per Kg of Prothrombin Complex Concentrate
Step 3	Intravenous administration of 10 mg of vitamin K1
Step 4	Urgent neurosurgical evaluation

Table 2. Standardized protocol within one hour after baseline CT scan of the head

Functional outcomes at 90 days were assessed by the modified Rankin Scale (where 0 indicates full recovery and 6 indicates death). Scores from 4 to 6 were considered poor outcomes, Table 3 shows modified Rankin Scale.

Score	Description
0	No symptoms at all
1	No significant disability despite symptoms; able to carry out all usual duties and activities
2	Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance
3	Moderate disability; requiring some help, but able to walk without assistance
4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability; bedridden, incontinent and requiring constant nursing care and attention
6	Death

Table 3. Modified Rankin Score

Statistical analysis

Statistical analyses were performed using the SAS System software package (SPSS). For univariate statistics, a conventional statistical test was used. Normally distributed data were expressed as mean±SD and were compared using the unpaired t test. Other data were expressed as median and range and were compared with nonparametric tests. Chi-square test and Fischer exact tests were used to determine associations between variables. A value of $P \leq 0.05$ was considered statistically significant.

End points

The primary end-point of the study was the evaluation of the reversal efficacy on the INR value: reversal was considered satisfactory if INR <1.5 30 mins after PCC administration. We also evaluated the following clinical end-points: long-term outcome with modified Rankin Scale, incidence of thrombotic events, perioperative bleeding of neurosurgical cases and mortality at 90 days.

Results

From January 2004 through January 2010, we observed 79 episodes of anticoagulation-related acute intracranial hemorrhage in a cohort of 76 consecutive patients at our Emergency Department. The median follow-up of each patient was at least three months. We were able to treat all patients with the same pharmacological approach (PCC and vitamin K1). PCC showed to be able to counteract the effect of warfarin in all patients; prompt reversal of OAT (INR<1.5) was obtained in 90% of cases within 30 minutes from administration. Average INR value was 2.99 (±1,05 SD) at presentation and decreased to 1,36 (±0,26 SD) 30 minutes after PCC administration (Figure 1 and table 4). Interestingly, among 8 cases who did not achieve INR <1.5, we observed a higher proportion of supra-therapeutic INR at diagnosis: in this subgroup of patients average INR was 4.49 (±1,23 SD) versus 2.69 (0,7 ± SD) in patients who corrected INR after PCC bolus (table 4). We did not observe any adverse event related to PCC or Vitamin K; particularly, vitamin K did not cause any anaphylactic reaction in our cohort of patients and PCC was not associated with any sort of adverse reaction. As regards thrombotic complications of PCC infusion, we observed eight (10%) non fatal thrombotic events: one ischemic stroke at day 25 of hospitalization, seven pulmonary embolisms respectively at days 14, 10, 3, 5, 5, 30 and 5 of hospitalization.

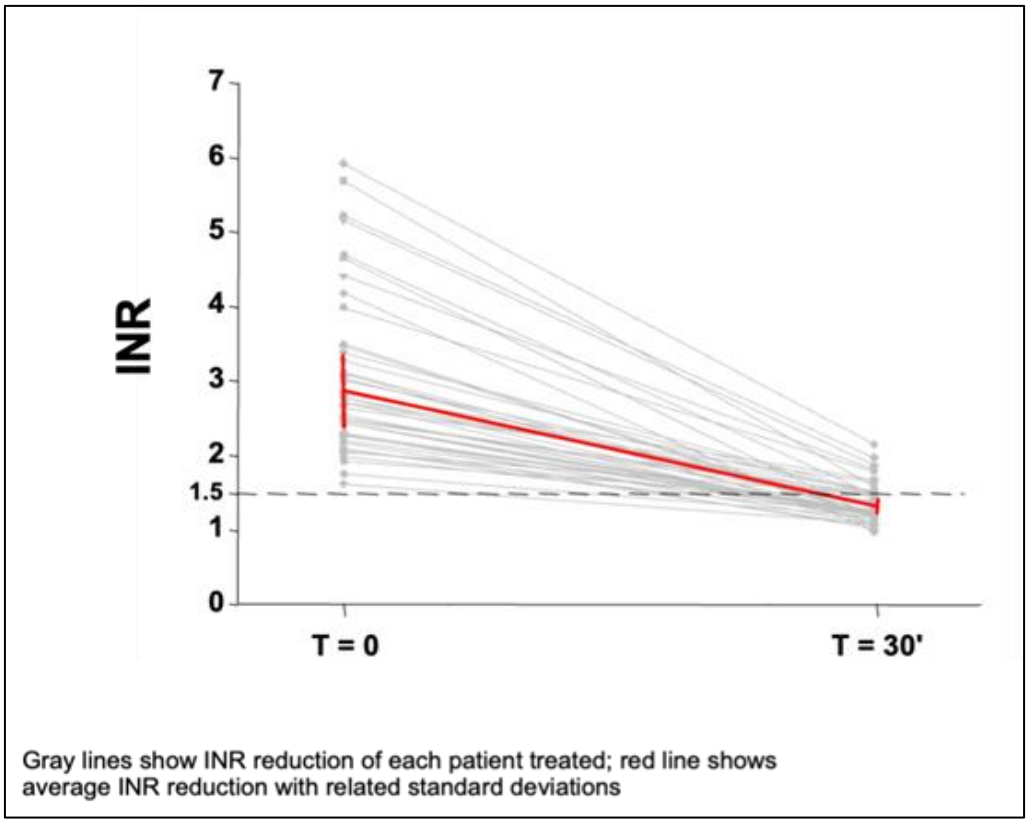

Figure 1: correction of INR in 79 AIH treated with Uman Complex

	Response Rate	Initial average INR (SD)	Average INR 30 min after PCC administration (SD)
Overall cases (79/79)	100%	2.99 (1.05)	1.35 (0.26)
Cases with INR < 1,5 30' after PCC bolus	71/79 (90%)	2.69 (0.7)	1.26 (0.16)
Cases with INR > 1,5 30' after PCC bolus	8 /79 (10%)	4.49 (1.23)	1.80 (0.20)
SD = Standard Deviation			

Table 4: Relevance of initial INR to achieve INR <1.5

Intracranial hemorrhage itself and the clinical state of patients can justify such a high incidence of thrombotic events rather than single PCC administration. We underline that all patients received low molecular weight heparin at prophylactic dosage as soon as possible during their hospitalization. All patients restarted anticoagulation not before 30 days after the previous ICH. Three patients had an intracranial hemorrhagic relapse after resuming oral anticoagulant therapy; an 85 year-old man with parossistic atrial fibrillation, an 83 year-old man with chronic atrial fibrillation and a 73 year-old man with mechanic mitral valve and a history of previous cardioembolic stroke relapses occurring within six months after the first intracranial bleeding. Correlation among recorded patients' variables and mortality rate at 90 days was sought. Although hypertension is a well-known risk factor for intracranial hemorrhage, surprisingly in our cohort a history of prior hypertension was associated with favorable outcome at univariate and multivariate analyses ($p<0.0003$). Similarly, a history of diabetes mellitus ($p<0.023$) and cerebral vasculopathy ($p<0.003$) seemed to be protective in terms of mortality at univariate analysis but not at multivariate analysis. (table 5 and 6).

Characteristics	Died within 3 Months (31 hemorrhages)	Survived for 3 Months (48 hemorrhages)	All intracranial hemorrhages	P value
Age (mean)	78.9	76.8	77.6	0.4 for age > 75 years
Male	19	26	45	0.69
INR (mean)	3.22	2.77	3	0.02 for INR>2
Dangerous drug association	3	9	12	0.4
Recent trauma	10	25	35	0.11
Hypertension	18	44	62	0.000381
Diabetes	4	17	21	0.023216
Cerebral vasculopathy	11	33	44	0.003503
Cholesterol mg/dL	174	171	173	0.55
Follow up at specialized OAT clinic	28	41	69	0.83
INR after PCC administration	1.38	1.33	1.35	0.96
Thrombotic events	2	6	8	0.86

Table 5: Clinical characteristics stratified by outcome in 79 patients with anticoagulant-associated ICH

Variable	Died Within 3 Months (31 hemorrhages)	Survived for 3 Months (48 hemorrhages)	Odds Ratio (95% Confidence Interval)	P-Value
Hypertension	18	44	0.04 (0.005-0.343)	0.000381
Diabetes	4	17	0.2 (0.05-0.343)	0.023216
Cerebral vasculopathy	11	33	0.21 (0.078-0.569)	0.003503

Table 6: Variables affecting case-fatality and mortality rate at three months in a multivariate analysis

All patients received urgent neurosurgical evaluation at diagnosis in the Emergency Department; 18 patients needed emergency neurosurgical evacuation of their subdural hematoma, without perioperative bleeding, except one patient who showed a relapse of bleeding a few days after neurosurgery. The clinical impact of rapid PCC administration in terms of functional physical recovery was quantified by the Rankin Scale. The Rankin score was assessed at diagnosis, at discharge and at three months' follow up visit. Among 48 patients still alive at three months, 35 (73%) showed a Rankin score ≥4 at diagnosis, 24 (50%) at discharge and only 13 (27%) at three months. These data reveal a remarkable margin of improvement and make a rapid treatment mandatory. (Figure 2)

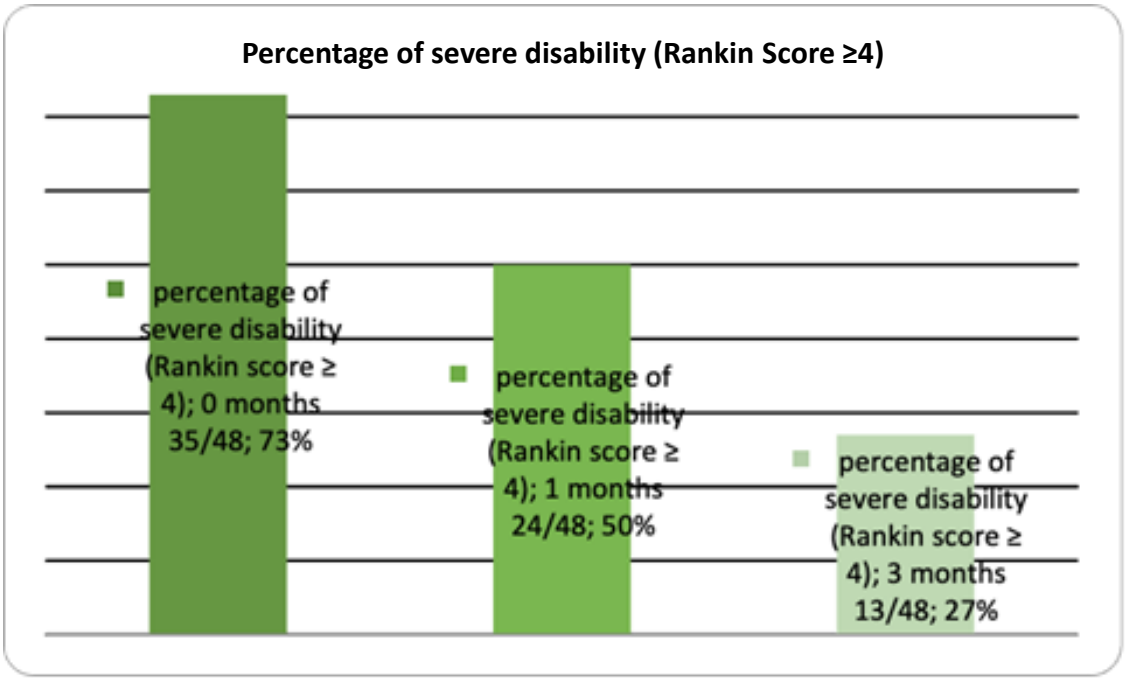

Figure 2: Functional outcome in 48 patients alive at three months.

As regards drug interactions, only two patients had taken acetyl salicylic acid or diclofenac shortly before AIH. We did not find any significant association between SSRI and mortality rate in our cohort. History of trauma within 15 days before AIH was extremely high in our cohort study; 35/79 (44%) patients reported a fall in recent anamnesis. This piece of data highlights that the question of falls in elderly persons is of paramount importance during management of VKAs therapy; however, in our cohort we could not find any significant association between falls and mortality rate.

Discussion

Several neuroradiological studies demonstrated that spontaneous intracranial hemorrhages expand over time owing to bleeding from rupture of small penetrating arteries. The management of acute intracranial hemorrhages is based upon the consciousness that a fast intervention may reduce hemorrhage volume and clinical impact on long-term disability and mortality. Despite wide and consolidated use of antivitamin K agonists and doctors' awareness of potentially life-threatening consequences of oral anticoagulant therapy, no well designed randomized clinical trial has so far been devised in order to assess the best treatment options for anticoagulation reversal. Thus, considerable differences of therapeutic strategies have been observed among intensive care units in different countries. Intravenous administration of vitamin K is a well known therapy for this subset of patients, but it requires almost 4-6 hours to work. Use of fresh frozen plasma (FFP) is an option widely used in USA but with many drawbacks: transfusion of FFP requires at least 30 minutes' thawing before administration and the volume needed to restore deficient coagulation factors may vary between 800 and 3500 ml, and the time lapse to correction of INR is unacceptable. Other pitfalls of FFP are volume overload, allergic reactions, transfusion related acute lung injury (TRALI), citrate toxicity and transmission of viral infections (9). Mayer SA et al. and Mannucci et al. demonstrated that recombinant activated factor VII (rVIIa) in patients with spontaneous acute cerebral hemorrhage reduces significantly hematoma expansion if administered within 6 hours after bleeding onset but mortality and functional outcome were not modified (10,11). There are small case series of patients with warfarin associated intracranial hemorrhage treated with rVIIa; all these studies reported faster correction of INR but only the study of Roitberg et al. reported an improved outcome (12). Furthermore, there are concerns about the efficacy of a single rVIIa dose on reverting warfarin-related coagulopathy and about safety for potential thromboembolic adverse events (13,14). Several case series of rapid reversal of VKAs with PCCs alone reported correction of INR faster than FFP in the setting of warfarin-related intracranial hemorrhage. So far, all studies available have demonstrated that PCCs are faster than FFP in INR normalization, but there is no evidence of outcome improvement.

Our study represents a "real world" picture of AIH management in an Italian community hospital. It shows that a standardized protocol to rapidly reverse INR prolongation and maintain normal values over time is feasible and easy to carry out. It also suggests that the faster the INR correction, the fewer the clinical consequences. Despite literature alerts, in our hands no adverse reactions directly attributable to vitamin K intravenous administration were observed and this study confirmed the rapidity and especially the safety of a specific aPCC in reverting VKAs coagulopathy.

Notwithstanding regular preventive low molecular weight heparin administration, we observed a rather high incidence of non fatal thromboembolic complications (10% of all cases), which was constituted by patients particularly prone to develop thrombosis due to underlying disease and to VKAs suspension. In conclusion our experience confirms the safety and feasibility of concomitant administration of vitamin K and PCC in the emergency setting of AIH. These data maintain a precious value if we consider that there is a notable underuse of PCC by clinicians in the setting of AIH, probably owing to the fear of thrombotic complications, of inadequate knowledge of PCCs and maybe of the multidisciplinary nature of AIH treatment. There is a pressing necessity for well-designed collaborative randomized studies to evaluate the best treatment option of the AIH, one of most common iatrogenic complications of clinical practice.

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