

Recombinant factor VIIa and prothrombin complex concentrates to treat bleeding episodes in hemophilic patients with inhibitors: a Systematic Review

Abstract

Objective: To determine the clinical efficacy of rFVIIa and aPCC to treat mild-to-moderate bleeding episodes in hemophilic patients with inhibitors.

Methods: Systematic review of therapeutic alternatives for the treatment of mild-to-moderate bleeding in hemophilic patients with inhibitors. The primary outcome was cessation of bleeding or therapeutic failure between the first 9 to 12 hours. Two authors in an independent way assessed the clinical trials (eligibility and risk of bias) and extracted the data. No meta-analysis was performed because of the lack of common results and comparisons in the included trials.

Results: Twenty-two articles were identified and two cross-over RCTs with low risk of bias were included. One of the RCTs establishes greater clinical efficacy of rFVIIa at 9 hours, and the other one, that there are no differences between the two strategies 12 hours after they were applied. The clinical efficacy of one RCT was evaluated in terms of the use of rescue medication, and in the other one as an algorithm that evaluated pain and mobility. There were no clinical trials about the biotechnology drug manufactured in Russia named Coagil®-VII, just was found one poster with a series of ten cases that reported success in four patients.

Conclusion: The clinical efficacy for rFVIIa fluctuates between 84-91% and for aPCC, between 64-80%. There is no valid evidence in the literature to determine the clinical efficacy of the biotechnological rFVIIa manufactured in Russia, which appears to be much lower than that of rFVIIa and aPCC.

Keywords: hemophilia A, hemophilia B, blood coagulation factor inhibitors, factor VIIa, generic drugs, blood coagulation

Introduction

Hemophilia is caused by a hereditary deficiency of factor VIII (FVIII) or IX (FIX), and it is classified as severe, moderate or mild, based on factor coagulant activity.^{1,2} Treatment aim, prophylactic or on-demand, is to avoid bleedings and their complications by applying coagulation factors. Purity of these concentrates increased since the 1980s, and procedures were developed that allow viral inactivation to prevent the transmission of infections such as HIV and Hepatitis C.³

Subsequently, concentrates of recombinant factors (without human proteins) were developed, which are part of current clinical practice. The immune system of some patients can recognize these factors as a foreign protein and produce antibodies called inhibitors, because they inhibit the activity of the administered factor. There are several factors that can increase the risk of developing inhibitors: defects of the gene causing the inhibitors, ethnicity, family history of hemophilia, among others.⁴

The treatment of a bleeding episode of a hemophilic with inhibitors depends on the level of antibodies (inhibitors). Although some hemophiliacs with low levels of inhibitors can be treated with standard concentrates, most often have inhibitors that destroy FVIII or infused FIX, so medications have been developed to treat these patients. Initially, these were based on human plasma, such as

Volume 6 Issue 3 - 2018

Jaime E Ordóñez,¹ Arlex U Palacios²

¹Lecturer at Universidad del Rosario, Colombia

²Professor at CES University, Colombia

Correspondence: Jaime E Ordóñez, Senior Researcher at True Consulting. Lecturer at Universidad del Rosario. Bogotá D, Carrera 27 A # 36 Sur-150, Int. 107, Envigado, Colombia, Tel (+57)301 390 3739 Email jaime.ordonez@trueconsulting.co

Received: April 17, 2018 | **Published:** June 04 2018

prothrombin complex concentrates activated (aPCC) or not activated (PCC), or porcine plasma.⁵ In the 1990s an alternative approach was proposed, developing a concentrate of recombinant FVIIa (rFVIIa) with high clinical efficacy.⁶

A recent study by the Cochrane Collaboration, which considered 67 patients in each arm, found that there were no statistically significant differences in clinical outcomes between rFVIIa and aPCC that were greater than 15%.⁷ Given that hemophilia is a rare disease and hemophilia with inhibitors represents only a fraction of this population, clinical trials evaluating these drugs are usually done with a small number of patients, which could explain the result of this study, since frequentist statistics methods often need large sample sizes to find statistically significant differences.

The objective of this study is to identify clinical efficacy of different treatment strategies for mild to moderate bleeding episodes in hemophilic patients with inhibitors, based on the best clinical evidence available in the scientific literature.

Methods

Search strategy and selection criteria

We conducted a search of randomized controlled trials (RCTs) without restriction of dates, languages, or age of patients in MEDLINE,

Embase and Cochrane Central Register of Controlled Trials databases, published until March 31, 2018. Search terms were hemophilia AND recombinant factor VIIa. Interventions evaluated were rFVIIa and concentrates derived from human plasma (concentrates of FVIII or recombinant human or high dose FIX, PCC and aPCC), which are the only bypass drugs available in the market for treatment of this population. Only one exclusion criteria considered were products derived from animals. A gray search was also made of the literature of posters in academic meetings that included these therapies, as well as the biotechnological product Coagil®-VII, discarding those that were duplicated as published research articles.

Primary clinical outcome was the cessation of bleeding, determined by changes in pain or mobility measured by means of some evaluation scale, by the volume of the hematoma evaluated radiologically between first 9 to 12 hours, or by therapeutic failure that forced changes the treatment. Secondary result was proportion of patients with adverse effects, such as thrombosis or allergic reactions.

Data collection and analysis

Data of the studies were taken independently by JO and AP, using standardized forms to assess risk of biases determined by the Cochrane Collaboration.⁸ Those studies were included in which the criteria of both researchers coincided, when there was a disagreement, these were discussed to make consensual decisions.

In case the way to evaluate clinical results was similar, a meta-analysis with a Bayesian model would be developed.^{9,10} Given that episodes of bleeding in hemophiliac patients with inhibitors should be controlled as early as possible in order not to risk their lives, a prudent amount of time was considered to take decisions about treatment success or the need to place rescue therapy. For this reason, a single evaluation point was considered in time that fluctuated between 9 and 12 hours, which in some cases coincided with the duration of the RCT. Primary outcome was treatment efficacy, established by the assessment of mobility, pain, or the need for rescue medication.

Results

Twenty-two articles whose full text was reviewed were identified, of which two RCTs with a low risk of bias were included for this systematic review;^{11,12} reasons for excluding the remaining 20 studies are summarized in Table 1.¹³⁻³² Two included studies were cross-over RCTs, one of which had two arms¹¹ and the other one, three,¹² and both were open trials. Study participants were adults and children. One RCT only included patients with hemophilia A¹¹ and the other included patients with hemophilia A and B,¹² although this latter did not specify the number of participants according to type of disease. In case of Coagil®-VII, only three posters were obtained, two reported laboratory results of coagulation tests, but without clinical results,³³⁻³⁴ the third reported the clinical results of a series of cases.³⁵

Astermak et al.¹¹ RCT enrolled 66 patients, of whom 14 were withdrawn before finishing treatment or they just received only one treatment, and in four participants was not taken full information.¹¹ RCT of Young admitted 42 patients and half of them completed the three treatment arms.¹² Andreeva case series enrolled ten patients with severe hemophilia A and inhibitors.³⁵ Two RCTs included in this systematic review compared rFVIIa with aPCC, and the Andreeva case series describes the clinical outcomes of Coagil®-VII (biosimilar, Generium, Russia).

Table I Reasons for exclusion of clinical trials to the systematic review about clinical efficacy of rFVIIa and aPCC for bleeding control in patients with hemophilia and inhibitors

Author	Reason for exclusion
Shapiro et al. ¹³	Double-blind RCT of dosing: the comparator is not an alternative treatment.
Lusher et al. ¹⁴	Double-blind RCT of dosing: the comparator is not an alternative treatment.
Villar et al. ¹⁵	Dosage trial: the comparator is not an alternative treatment.
Santagostino et al. ¹⁶	Cross-over and open RCT comparing two different regimens of rFVIIa.
Kavakli et al. ¹⁷	Cross-over and open RCT comparing two different regimens of rFVIIa.
Konkle et al. ¹⁸	RCT that evaluates rFVIIa for prophylaxis of bleeding not for treatment.
Bysted et al. ¹⁹	RCT that evaluates the bioequivalence of two rFVIIa presentations.
Pruthi et al. ²⁰	Open-label RCT comparing two different regimens of rFVIIa in patients with hemophilia undergoing major surgery.
Steen Carlsson et al. ²¹	Economic evaluation done with secondary information from other RCTs.
Møss et al. ²²	Dosage RCT on a pegylated presentation of rFVIIa.
Skolnick et al. ²³	RCT that evaluates rFVIIa for the control of bleeding induced by clopidogrel.
Morfini et al. ²⁴	RCT that evaluates the pharmacokinetics of two different presentations of rFVIIa.
Mahlangu et al. ²⁵	Dosage trial: the comparator is not an alternative treatment.
De Paula et al. ²⁶	Dosage trial: the comparator is not an alternative treatment.
Ljung et al. ²⁷	RCT comparing two different regimens of rFVIIa.
Golor et al. ²⁸	RCT that evaluates the pharmacokinetics of a rFVIIa presentation with albumin.
Faranoush et al. ²⁹	RCT that evaluates the bioequivalence of two rFVIIa presentations.
Lentz ³⁰	RCT comparing two different regimens of rFVIIa.
Faranoush et al. ³¹	RCT that evaluates the bioequivalence of two rFVIIa presentations.
Mahlangu et al. ³²	RCT that evaluates immunogenicity of changes in the amino acid sequence of rFVIIa.

In Astermak et al.¹¹ RCT, dose of aPCC was 75 to 100IU/kg in a single intravenous bolus (IV), and dose of rFVIIa was 90 to 120mcg/kg as an IV bolus that was repeated after two hours.¹¹ In Young et al.¹² RCT, dose of aPCC was 75IU/kg in a single bolus IV, dose of rFVIIa was 90mcg/kg IV that was repeated at three and six hours in one arm of the ECA, and in the other arm was of 270mcg/kg in a single IV bolus, followed by two placebo applications at three and six hours.¹² The beginning of the treatments was done in the first two hours after the bleeding started. In both RCTs, the results were measured subjectively with indicators such as global evaluation, cessation of pain, improvement of motility and need for additional treatment.

Risk of bias in the studies only applies to RCTs, since Andreeva's study is about a series of cases. In their results, the authors point out that they are patients who were always treated with NovoSeven® (rFVIIa, Novo Nordisk, Denmark) and to whom the medication was exchanged for a rFVIIa biotechnology called Coagil®-VII. That study included ten patients, of whom four had resistance to treatment and two had severe allergic reactions. Due to therapeutic failures and

adverse events, patients had to be hospitalized and NovoSeven® was applied again, obtaining a good therapeutic response. These results were not included in this meta-analysis because that technique was developed to evaluate two or more analytical studies, and that study is descriptive.³⁵

Regarding the generation of randomization sequence, randomization in Astermark et al.¹¹ RCT became associated with the first hemorrhagic event in a block of participants divided equally, but authors do not describe the method of random assignment.¹¹ In Young et al.¹² RCT, six treatment sequences were generated by permutation of the three strategies evaluated.¹² Randomization concealment was not ideal in both RCTs because these were open trials, likewise, Young et al.¹² RCT does not provide details of concealment of randomization code assignment when comparing the two regimens of rFVIIa. Similarly, due to differences between the two products (physical aspect and volume required for the application), it was not possible to blind the assigned treatment, although in the Young et al.¹² RCT blinding was made between both rFVIIa strategies (three active boluses versus one active and two placebo boluses).

On the incomplete results data, Astermark et al.¹¹ RCT recruited 66 patients, of which 48 completed the protocol. This RCT had 14 patients who withdrew before initiating the protocol or who received treatment in only one arm.¹¹ In Young et al.¹² RCT, half of the 42 patients recruited completed the protocol. Fourteen patients were randomized but did not receive treatment, three were withdrawn due to noncompliance, two because the study was closed and there were no episodes of bleeding, and one patient was transferred to another hospital center that did not participate in the study.¹² Regarding information reported, no discrepancies were found between the methods and results sections of both RCTs. Results and follow-up time are those commonly used in this type of trial and were proposed as outcome measures for this systematic review.

Regarding other possible sources of bias, Young et al.¹² RCT had a subjective measure as the main outcome, and any outcome measure reported by patients have a risk of bias.¹² The use of analgesics was allowed in both RCTs, but there was a potential interference from patients to interrupt them to make a subjective assessment of pain. Astermark et al.¹¹ RCT evaluated the distribution of analgesics in both treatment groups.¹¹ In the way of measuring results, Astermark et al.¹¹ RCT defined an effective response through dichotomous categories of effective or partially effective versus ineffective or ineffective. Young et al.¹² RCT developed an algorithm that took pain and mobility scores into account.

Given that Astermark et al.¹¹ and Young et al.¹² trials are RCTs, their sample sizes are equal, but the number of successes obtained for each strategy is different. In the Astermark et al.¹¹ RCT, 45 patients were evaluated at 12 hours, with 38 successes in the rFVIIa arm and 36 in the aPCC arm;¹¹ in Young et al.¹², 22 patients were evaluated at nine hours and success was considered not to administer rescue medication, the rFVIIa arm reported 20 successes and that of aPCC reported 14 successes.¹² Based on both RCTs, clinical efficacy for the treatment of mild to moderate bleeding in patients with hemophilia and rFVIIa inhibitors ranges from 84.4–91.7% and that of aPCC, between 63.6–80%, between first 9 to 12 hours after starting treatment, which is the usual time before repeating or increasing the dose of any of these two treatment strategies.^{11,12}

Regarding the clinical efficacy of biotechnology of rFVIIa

manufactured in Russia, only is available the information of Andreeva series of cases,³⁵ in which they state that ten patients to whom Coagil-VII® was applied, there was therapeutic failure in four patients and allergic reaction in two patients, so they had to make the change to NovoSeven®, obtaining a good clinical response in those patients.

Discussion

This systematic review found only two head-to-head RCTs of rFVIIa and aPCC, in which it was observed that the clinical efficacy to control bleeding in patients with hemophilia and rFVIIa inhibitors ranges from 84%– 91% and that of aPCC, between 64 %–80%. Evidence shows a slight clinical superiority of rFVIIa, although the low number of patients included in both RCTs may affect variation of such results.^{11,12} Selection of these two RCTs coincides with the meta-analysis of Matino et al.⁷, which concludes that these are the two studies with the least risk of bias, which generates greater validity to this conclusion when considering two RCTs that, in addition, they have similar conclusions.

It should be mentioned that both RCTs have several weaknesses; first, was the amount of losses they had, which, because they are RCTs, affects treatment strategies evaluated equally. Regarding the way to evaluate results, it should be noted that there is still no validated method to measure joint bleeding, which is why pain and mobility are used as outcome variables in all RCTs that evaluate this pathology. Also, there is no consensus on when to evaluate the effectiveness of these medications to control bleeding, but it is considered that a time between 9 and 12 hours is relevant to take decisions about the need to change therapy, because a longer time to evaluate therapeutic efficacy of these strategies, could put the lives of patients at risk.

Young et al.¹² RCT used a composite algorithm to evaluate the patients' judgment to determine clinical efficacy, which may present technical difficulties in reproducing it, for this reason the use of rescue medication as a result measurement, which is easily reproducible, was considered, and this represents a therapeutic failure. One aspect that was not considered in this systematic review is the viral safety of both strategies, since the aPCC is manufactured with plasma derivatives, while the rFVIIa is of synthetic manufacture. Likewise, it should be considered that the aPCC contains traces of factor VIII, which could induce an immune reaction in this population, something that is intended to be avoided in hemophiliac patients who are candidates for induction of immunotolerance treatment (ITI). Another weakness that both RCTs may have^{11,12} is that there is no blinding of the exposure, but this is not possible given the difference in the presentations and dosing of rFVIIa and aPCC.

One weakness of all RCTs done in populations with orphan diseases is the small number of patients in whom they are performed, precisely because of the low prevalence of these. This situation tends to affect the conclusions of their statistical analyzes, since the approach of frequentist statistics that needs a large amount of population to find statistically significant differences is usually used. This could be ignored if one of the comparators is placebo, in which case it would be possible for a small population to be sufficient to establish differences with statistical significance. But in this case this approach is not possible since it would violate the ethical principle of justice in RCTs, which establishes that all participants must receive the minimum treatment that has shown clinical results.

Similarly, a strategy to increase size of the population is to use the

cross-RCT model, in which all patients are exposed to different arms of a trial. This kind of trial is possible when results are observed in a short period of time and if the strategies studied have a washout period that is also short, without endangering integrity of patients. These conditions are met in clinical evaluation of rFVIIa and aPCC, because the half-life of both drugs is relatively short and clinical results can be observed in a short period of time.

Considering theoretical debates that have been presented about limitations of frequentist statistics, such as the need for large sample sizes to generate conclusions or to use an arbitrarily *p* value,³⁶ among others, there are other approaches that could be used to analyze this information, such as those of the Bayesian statistic. In analysis of results, Bayesian method considers previously known information of the object of study to determine *a priori* probabilities, which is completely logical since there is a body of knowledge that cannot be ignored when evaluating current information, situation which is only considered by frequentist statistics when calculating the sample size, but not when analyzing results.

These limitations of frequentist statistics may explain that meta-analysis published by Matino et al.⁷ did not find statistically significant differences between the efficiencies of rFVIIa and aPCC. Hypothesis of that study, under a frequentist approach, was that the difference between both strategies should be at least 15%, given that no statistically significant difference was observed, assumed that both efficiencies were similar. That is, theoretically there could be a difference in clinical efficacy of 14% between both treatment strategies, but the data analysis under a frequentist statistical approach would not allow to identify such a difference.

Likewise, these are drugs that have a high cost, and changing treatment due to clinical failure would mean that the initial therapeutic effort, both health and economic, was in vain. That is, although the difference in therapeutic efficacy between both drugs is not greater than 15%, as established by Matino et al.⁷, a difference in efficacy that fluctuates between 10-14% in favor of either of the two strategies cannot be considered small, especially when taking into account such important factors as the short period of time in which bleeding should be controlled without putting patient's life at risk, as well as the high prices of both strategies. Treuer et al.³⁷ did a Bayesian meta-regression comparing rFVIIa and aPCC in patients with hemophilia and inhibitors. With this statistical approach, the authors concluded that rFVIIa was more effective than aPCC after 12, 24 and 36 hours.³⁷

Finally, regarding the biotechnology of rFVIIa called Coagil®-VII, only three posters were identified through gray literature search. Two of them evaluated their results by means of coagulation tests that are proxy variables.³³⁻³⁴ This affects the validity of those studies, considering that all RCTs on rFVIIa and aCPP express their results in clinical terms, it is not possible to compare them with laboratory results, since the latter do not reflect medication clinical effectiveness, information that is necessary to take decisions. That is, no argumentation was found that justifies avoiding measurement or publication of clinical results of this biotechnological medicine, which would affect the validity of such results. On the other hand, third poster reports clinical results of a series of ten patients, in which authors conclude that there was only clinical efficacy in four of them when using the biosimilar drug.³⁵ That is, based on that study, clinical efficacy of this biosimilar would be approximately 40%, which is less than half that used for the *a priori* probabilities of rFVIIa and aPCC, which was calculated when considering several RCTs. This efficacy

is low compared to that of its comparators, which would endanger integrity of the patients, because if a mild to moderate bleeding is not promptly controlled on an outpatient basis, the risk of developing hemarthrosis is increased, as well as its management in an inpatient way, which significantly increases the cost of treatment.

Conclusion

The clinical efficacy to control bleeding in patients with hemophilia and inhibitors of rFVIIa fluctuates between 84%-91% and that of aPCC, between 64%-80%. Similarly, there is no valid evidence in bioscience literature to determine clinical efficacy of the biotechnological product Coagil®-VII, which is apparently much lower than that reported in several RCTs for rFVIIa and aPCC.

Acknowledgements

None.

Financial support

Author declare they did not receive any financial support.

Conflict of interest

Authors declare that there is no conflict of interest.

References

1. <https://www.wfh.org/en/>
2. White GC, Rosendaal F, Aledort LM, et al. Definitions in hemophilia. Recommendation of the scientific subcommittee on factor VIII and factor IX of the scientific and standardization committee of the International Society on Thrombosis and Haemostasis. *Thromb Haemost*. 2001;85(3):560.
3. Rizza CR, Spooner RJ, Giangrande PL, et al. Treatment of haemophilia in the United Kingdom 1981–1996. *Haemophilia*. 2001;7(4):349–359.
4. Dimichele D. Inhibitors: resolving diagnostic and therapeutic dilemmas. *Haemophilia*. 2002;8(3):280–287.
5. Hay CR, Baglin TP, Collins PW, et al. The diagnosis and management of factor VIII and IX inhibitors: a guideline from the UK Haemophilia Centre Doctors' Organization (UKHDCDO). *Br J Haematol*. 2000;111(1):78–90.
6. 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(6):912–918.
7. Matino D, Makris M, Dwan K, et al. Recombinant factor VIIa concentrate versus plasma-derived concentrates for treating acute bleeding episodes in people with haemophilia and inhibitors. *Cochrane Database Syst Rev*. 2015;(12):CD004449.
8. *Cochrane handbook for systematic reviews of interventions*. In: Higgins JPT, Green S, editors. The Cochrane Collaboration: Version 5.1.0 [updated March 2011]; 2011.
9. Smith TC, Spiegelhalter DJ, Thomas A. Bayesian approaches to random-effects meta-analysis: a comparative study. *Stat Med*. 1995;14(24):2685–2699.
10. Lu G, Ades AE. Combination of direct and indirect evidence in mixed treatment comparisons. *Stat Med*. 2004;23:3105–3124.
11. Astermark J, Donfield SM, DiMichele DM, et al. A randomized comparison of bypassing agents in hemophilia complicated by an inhibitor: the FEIBA NovoSeven Comparative (FENOC) Study. *Blood*. 2007;109(2):546–551.

12. Young G, Shafer FE, Rojas P, et al. Single 270 microg kg(-1)-dose rFVIIa vs. standard 90 microg kg(-1)-dose rFVIIa and APCC for home treatment of joint bleeds in haemophilia patient with inhibitors: a randomized comparison. *Haemophilia*. 2008;14(2):287–294.
13. Shapiro AD, Gilchrist GS, Hoots WK, et al. Prospective, randomized trial of two doses of rFVIIa (NovoSeven) in haemophilia patients with inhibitors undergoing surgery. *Thromb Haemost*. 1998;80(5):773–778.
14. Lusher JM, Roberts HR, Davignon G, et al. A randomized, double-blind comparison of two dosage levels of recombinant factor VIIa in the treatment of joint, muscle and mucocutaneous haemorrhages in persons with haemophilia A and B, with and without inhibitors. rFVIIa Study Group. *Haemophilia*. 1998;4(6):790–798.
15. Villar A, Aronis S, Morfini M, et al. Pharmacokinetics of activated recombinant coagulation factor VII (NovoSeven) in children vs. adults with haemophilia A. *Haemophilia*. 2004;10(4):352–359.
16. Santagostino E, Mancuso ME, Rocino A, et al. A prospective randomized trial of high and standard dosages of recombinant factor VIIa for treatment of hemarthroses in hemophiliacs with inhibitors. *J Thromb Haemost*. 2006;4(2):367–371.
17. 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, randomized, double-blind, cross-over trial. *Thromb Haemost*. 2006;95(4):600–605.
18. Konkle BA, Ebbesen LS, Erhardtse E, et al. Randomized, prospective clinical trial of recombinant factor VIIa for secondary prophylaxis in hemophilia patients with inhibitors. *J Thromb Haemost*. 2007;5(9):1904–1913.
19. Bysted BV, Scharling B, Møller T, et al. A randomized, double-blind trial demonstrating bioequivalence of the current recombinant activated factor VII formulation and a new robust 25 degrees C stable formulation. *Haemophilia*. 2007;13(5):527–532.
20. Pruthi RK, Mathew P, Valentino LA, et al. Haemostatic efficacy and safety of bolus and continuous infusion of recombinant factor VIIa are comparable in haemophilia patients with inhibitors undergoing major surgery. Results from an open-label, randomized, multicenter trial. *Thromb Haemost*. 2007;98(4):726–732.
21. Steen Carlsson K, Astermark J, Donfield S, et al. Cost and outcome: comparisons of two alternatives bypassing agents for persons with haemophilia A complicated by an inhibitor. *Thromb Haemost*. 2008;99(6):1060–1067.
22. Moss J, Roshholm A, Laurén A. Safety and pharmacokinetics of a glycoPEGylated recombinant activated factor VII derivative: a randomized first human dose trial in healthy subjects. *J Thromb Haemost*. 2011;9(7):1368–1374.
23. Skolnick BE, Shenouda M, Khutoryansky NM, et al. Reversal of clopidogrel-induced bleeding with rFVIIa in healthy subjects: a randomized, placebo-controlled, double-blind, exploratory study. *Anesth Analg*. 2011;113(4):703–710.
24. Morfini M, Jiménez-Yuste V, Eichler H, et al. Pharmacokinetic properties of two different recombinant activated factor VII formulations. *Haemophilia*. 2012;18(3):431–436.
25. Mahlangu JN, Coetzee MJ, Laffan M, et al. Phase I, randomized, double-blind, placebo-controlled, single-dose escalation study of the recombinant factor VIIa variant BAY 86–6150 in hemophilia. *J Thromb Haemost*. 2012;10(5):773–780.
26. de Paula EV, Kavakli K, Mahlangu J, et al. Recombinant factor VIIa analog (vatreptacog alfa [activated]) for treatment of joint bleeds in hemophilia patients with inhibitors: a randomized controlled trial. *J Thromb Haemost*. 2012;10(1):81–89.
27. Ljung R, Karim FA, Saxena K, et al. 40K glycoPEGylated, recombinant FVIIa: 3month, double-blind, randomized trial of safety, pharmacokinetics and preliminary efficacy in hemophilia patients with inhibitors. *J Thromb Haemost*. 2013;11(7):1260–1268.
28. Golor G, Bensen-Kennedy D, Haffner S, et al. Safety and pharmacokinetics of a recombinant fusion protein linking coagulation factor VIIa with albumin in healthy volunteers. *J Thromb Haemost*. 2013;11(11):1977–1985.
29. Faranoush M, Abolghasemi H, Toogeh G, et al. A comparison between recombinant activated factor VII (Aryoseven) and Novoseven in patients with congenital factor VII deficiency. *Clin Appl Thromb Hemost*. 2015;21(8):724–728.
30. Lentz SR, Ehrenforth S, Karim FA, et al. Recombinant factor VIIa analog in the management of hemophilia with inhibitors: results from a multicenter, randomized, controlled trial of vatreptacog alfa. *J Thromb Haemost*. 2014;12(8):1244–1253.
31. Faranoush M, Abolghasemi H, Mahboudi F, et al. A Comparison of Efficacy between Recombinant Activated Factor VII (Aryoseven) and Novoseven in Patients with Hereditary FVIII Deficiency with Inhibitor. *Clin Appl Thromb Hemost*. 2016;22(2):184–190.
32. Mahlangu JN, Welding KN, Lentz SR, et al. Changes in the amino acid sequence of the recombinant human factor VIIa analog, vatreptacog alfa, are associates with clinical immunogenicity. *J Thromb Haemost*. 2015;13(11):1989–1998.
33. Galstyan G, Zorenko V, Polyanskaya T, et al. Efficacy of the Russian biosimilar of rFVIIa koagil VII in hemophilic patients with inhibitor. *Haemophilia*. 2013;19(Suppl 2):47–48.
34. Galstyan G, Zorenko V, Polyanskaya T, et al. Comparison of the efficacy of two recombinant factor VIIa agents. *J Thromb Haemost*. 2011;9(Suppl 2):470.
35. Andreeva TA, Konstantinova VN. Adverse reactions using biosimilar of rFVIIa Coagil VII. 18th International Meeting Danubian League against Thrombosis and Haemorrhagic Disorders, Sarajevo. 2015;52:123.
36. Silva Ayçaguer LC, Muñoz Villegas A, Vázquez Fernández E. Debate sobre métodos frecuentistas vs bayesianos. *Gaceta Sanitaria*. 2000;14(6):482–494.
37. Treur MJ, McCracken F, Heeg B, et al. Efficacy of recombinant activated factor VII vs. activated prothrombin complex concentrate for patients suffering from haemophilia complicated with inhibitors: a Bayesian meta-regression. *Haemophilia*. 2009;15(2):420–436.