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[Intervention Review]

Recombinant factor VIIa concentrate versus plasma-derived concentrates for treating acute bleeding episodes in people with haemophilia and inhibitors

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ABSTRACT

Background

In people with haemophilia, therapeutic clotting agents might be recognised as a foreign protein and induce anti-factor VIII antibodies, known as 'inhibitors'. Drugs insensitive to such antibodies, either recombinant or plasma-derived, are called factor VIII 'by-passing' agents and used for treatment of bleeding in people with inhibitors.

Objectives

To determine the clinical effectiveness of recombinant factor VIIa concentrate compared to plasma-derived concentrates for treating acute bleeding episodes in people with haemophilia and inhibitors.

Search methods

We searched the Cochrane Cystic Fibrosis and Genetic Disorders Group Coagulopathies Trials Register which comprises references identified from comprehensive electronic database searches and handsearches of relevant journals and abstract books of conference proceedings.

Date of the most recent search of the Group's Coagulopathies Trials Register: 23 September 2015.

Selection criteria

Randomised and quasi-randomised controlled clinical trials comparing recombinant factor VIIa concentrate to human plasma-derived concentrates (high-dose human or recombinant factor VIII or factor IX concentrate; non-activated prothrombin complex concentrates; activated prothrombin complex concentrates) in people with haemophilia. Comparisons with animal-derived products were excluded.

Data collection and analysis

Two authors independently assessed the trials (eligibility and risk of bias) and extracted data. No combined meta-analyses were performed due to the unavailability of outcomes and comparisons common to the included trials.

Recombinant factor VIIa concentrate versus plasma-derived concentrates for treating acute bleeding episodes in people with haemophilia and inhibitors (Review)

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Main results

A total of 15 trials were identified, two of which (with data for a total of 69 participants) were eligible for analysis. Both trials showed methodological flaws and did not show superiority of one treatment over the other. Both the treatments showed that recombinant factor VIIa and activated prothrombin complex concentrate appeared to have a similar haemostatic effect in both trials, without increasing thromboembolic risk.

Authors' conclusions

Based on the separate analysis of the two available randomised trials, recombinant factor VIIa and activated prothrombin complex concentrate were found to be similar in efficacy and safety. However, there is a need for further, well-designed, adequately-powered, randomised controlled trials to assess the relative benefits and risks of using recombinant factor VIIa compared to human plasma-derived concentrates in people with haemophilia with inhibitors. It is advisable that researchers in the field define commonly agreed objective outcome measures in order to enable the pooling of their results, thus increasing the power of comparisons. To date, data could not be combined in a formal meta-analysis. For the same reason reporting concordant and discordant pairs in cross-over trials is recommended.

PLAIN LANGUAGE SUMMARY

Recombinant (non-human) factor VIIa clotting factor concentrates versus plasma concentrates for acute bleeds in people with haemophilia and inhibitors

Review question

We wanted to find evidence on the effectiveness of recombinant factor VIIa (containing no human proteins) as compared to concentrates derived from plasma for treating acute bleeding episodes in people with haemophilia with inhibitors.

Background

Haemophilia is an inherited bleeding disorder caused by a lack of a clotting factor and is characterised by bleeding into the joints. It is treated by injecting a drug containing the missing clotting factor into veins. In some individuals with haemophilia, this factor is seen by the body as a foreign protein when it is injected and the body produces an antibody (inhibitor) that destroys the factor. In this way these people become resistant to treatment. Once someone with haemophilia develops an inhibitor, they are treated to remove the antibody (immunotolerance induction) and for acute bleeding episodes. Treatment for bleeding episodes is with one of two available bypassing agents, recombinant activated factor VIIa (Novoseven[®]) or human activated prothrombin complex concentrate (FEIBA[®]). It is not known if one of these products is better than the other. We searched for trials comparing the effectiveness (time until bleeding stops, effect on joint motion, need for re-treatment) and safety of Novoseven[®] and FEIBA[®] in people with haemophilia with inhibitors during episodes of acute bleeding.

Search date

The evidence is current to: 23 September 2015.

Study characteristics

The review included two trials with 69 people (aged one to 55 years) with severe haemophilia with inhibitors. Both trials compared recombinant factor VIIa with activated prothrombin complex concentrate and people were selected for one treatment or the other randomly.

Key results

We found two clinical trials comparing Novoseven[®] and FEIBA[®]. The trials did not show a difference in how well the two products worked and both were tolerated equally well with no clotting complications. We conclude that both recombinant factor VIIa and plasma-derived concentrates can be used to treat bleeds in people with haemophilia and inhibitors.

Quality of the evidence

There were some major problems with regards to the way both trials were designed, in relation to knowing which treatment group each person was in (both before the trial was started and during) and also how missing results were handled.

BACKGROUND

Description of the condition

Haemophilia is an inherited disorder where affected individuals suffer from excessive bleeding. It is inherited as an X-linked disorder, but in around a third of all cases no family history is present. People with haemophilia develop spontaneous bleeding into joints and suffer excessive bleeding after injury or surgery which can be hazardous unless appropriately managed in expert centres. Two main types are recognised due to either a deficiency of factor VIII (FVIII) (haemophilia A) or of factor IX (FIX) (haemophilia B). The prevalence is similar worldwide and for haemophilia A is 1 in 10,000 and for haemophilia B is 1 in 60,000 births (Mannucci 2001).

The severity of the phenotype depends on the baseline concentration of the clotting factor. The severity of haemophilia has been defined by the International Society for Thrombosis and Haemostasis as:

- severe, where the factor is less than 0.01 units per millilitre (u/ml);
- moderate, where the factor ranges from 0.01 u/ml to less than 0.05 u/ml; and
- mild, where the factor is greater than 0.05 u/ml (White 2001).

Spontaneous bleeding into joints is seen primarily in people with severe haemophilia.

Description of the intervention

The mainstay of treatment in bleeding disorders due to factor deficiency is the correction of the defect by the intravenous infusion of the appropriate clotting factor. For haemophilia, initially in the 1960s this consisted of the infusion of fresh frozen plasma (haemophilia A and haemophilia B) and cryoprecipitate (haemophilia A) and was followed in the 1970s by the introduction of FVIII (haemophilia A) or FIX (haemophilia B) concentrates. Over the last 30 years the purity of concentrates has increased; and since 1985 viral inactivation procedures were introduced to eliminate blood product-transmitted infections such as HIV and hepatitis C (Rizza 2001). At the beginning of the 1990s recombinant factor concentrates (that do not contain human proteins) were developed and these have entered clinical practice (UKHCDO 2003).

In some people with haemophilia the administered factor is recognised as a foreign protein and anti-FVIII or anti-FIX antibodies are produced. These antibodies are referred to as inhibitors when they inhibit the activity of the administered factor. The reported prevalence of inhibitors in haemophilia A varies enormously from 3.6% (Yee 1999) to 32% (Kreuz 2002). The incident rate of inhibitors is much lower in haemophilia B than in haemophilia A, but inhibitor

treatment in haemophilia B is hampered by complications due to immuno-complex mediated renal damage (Ewenstein 1997). The risk of developing an inhibitor has been found to be associated with: the causative genetic defect (Dimichele 2002), with gene deletions having the highest risk of developing an inhibitor (Goodeve 2003); ethnicity; family history of haemophilia with or without inhibitors; the length and intensity of exposure to factor concentrates; the age at first exposure; and the occurrence of a trigger event (i.e. bleeding, surgery or infections). Other reasons for the varying prevalence of inhibitors observed in different published reports may be the laboratory method for measuring the inhibitor as well as the frequency of inhibitor testing. The lower prevalence of gene deletions in haemophilia B partly explains the lower rate of inhibitor development (DiMichele 2007).

There are two key elements in the treatment of people with haemophilia with inhibitors. The first, which is addressed by this review, is the treatment of the individual to arrest the acute bleeding. The second element is treatment to eliminate the inhibitor (immune tolerance induction), which is the subject of another Cochrane review (Athale 2014).

How the intervention might work

The acute treatment of someone with haemophilia and an inhibitor depends on the level of the antibody or inhibitor that is measured *in vitro* and is quantified in Bethesda units. A Bethesda unit is a measure of inhibitor activity and is the amount of inhibitor that will inactivate 50% or 0.5 unit of a coagulation factor in an activated partial thromboplastin time (aPTT)-based coagulation factor assay following a two-hour incubation period in an imidazole buffer diluted sample. Although some people with haemophilia with low levels of inhibitor can be treated with standard concentrates, in practice most have inhibitors that destroy the infused FVIII or FIX and other products have been developed to treat these individuals. These are based on human plasma such as activated prothrombin complex concentrates (aPCC) (brands available are FEIBA[®] and Autoplex[®]) or non-activated prothrombin complex concentrates (PCC) or animal plasma such as Hyate-C[®] (FVIII prepared from porcine plasma, can be used in people with haemophilia with no antibodies to porcine FVIII) (Hay 2000). A more recent alternative approach has been the use of recombinant FVIIa concentrate (rFVIIa) (NovoSeven[®]), which was introduced early in the 1990s and shown to be highly effective but also associated with a relatively high cost (Hedner 2000). Mainly aPCC exerts its effect by providing activated factor IX and X, which are able to produce a significant amount of thrombin without any requirement for FVIII (Thomas 1977); noticeably, aPCC is not expected to be active in people with factor IX deficiency. At a pharmacological concentration, rFVIIa is able to directly activate thrombin when bound to tissue factor or to activate factor Xa on the surface of activated platelets (Hedner 2000). The difference in the mechanism of action of the two compounds makes it reason-

able to switch the non-responding individual from one treatment to the other, and to assess the efficacy and safety of the combination of the two drugs.

Why it is important to do this review

This review investigates which is the most effective treatment of acute bleeding in people with haemophilia with inhibitors.

OBJECTIVES

To determine the clinical effectiveness of rFVIIa in comparison to PCC or aPCC for treating acute bleeding episodes in people with haemophilia with inhibitors.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised (RCTs) and quasi-randomised controlled clinical trials.

Types of participants

Children and adults with haemophilia, of all degrees of severity diagnosed by decreased blood levels of functional procoagulant FVIII or FIX and with FVIII or FIX inhibitors of any titre.

Types of interventions

Recombinant FVIIa concentrate (rFVIIa) compared to human plasma-derived concentrates (high-dose human or recombinant FVIII or FIX concentrate; PCCs; aPCC). Comparisons with animal-derived products were excluded.

Types of outcome measures

Primary outcomes

1. Early cessation of bleeding measured by
 - i) changes on any subjective or objective pain and mobility scale or
 - ii) by the volume of haematoma assessed radiologically at any point in the first 48 hours

Secondary outcomes

1. Number of participants requiring additional or alternative treatment
2. Number of participants with adverse effects (thromboses; allergic reactions)
3. Correction of abnormal haemostatic laboratory test results

Search methods for identification of studies

No restrictions based on dates, language or publication status were imposed.

Electronic searches

Relevant trials were searched for on the Group's Coagulopathies Trials Register using the terms: (haemophilia A AND factor VIIa) OR (haemophilia B AND factor VIIa) OR (haemophilia general AND (recombinant factor VIIa OR factor VIIa))

The coagulopathies register is compiled from electronic searches of the Cochrane Central Register of Controlled Trials (CENTRAL) (updated each new issue of *The Cochrane Library*), weekly searches of MEDLINE and the prospective handsearching of one journal - *Haemophilia*. Unpublished work is identified by searching the abstract books of four major conferences: the European Haematology Association conference; the American Society of Hematology conference; the British Society for Haematology Annual Scientific Meeting; and the Congress of the World Federation of Haemophilia. For full details of all searching activities for the register, please see the relevant section of the [Cochrane Cystic Fibrosis and Genetic Disorders Group Module](#).

Date of the most recent search of the Cystic Fibrosis and Genetic Disorders Group's Coagulopathies Trials Register: 23 September 2015.

Data collection and analysis

Selection of studies

In the 2010 update, two trials were found to be eligible for inclusion ([Astermark 2007](#); [Young 2008](#)). Additional data were obtained from trial authors for the 2015 update and included in the review ([Astermark 2007](#); [Young 2008](#)).

For the references found when updating the review after October 2007, two authors (AI, DM) independently selected the trials to be included in the review. When disagreement arose on the suitability of a trial for inclusion in the review or on its quality, we attempted to reach a consensus by discussion.

Data extraction and management

Two authors (AI, DM) independently extracted data using standard data acquisition forms. When disagreement arose on the suitability of a trial for inclusion in the review or on its quality, we reached a consensus by discussion.

Assessment of risk of bias in included studies

Two authors (AI, DM) assessed the risk of bias of each trial. In particular, they examined details of the randomisation method, whether the trial was blinded, whether intention-to-treat analyses were possible from the available data and if the number of participants lost to follow up or subsequently excluded from the study was recorded. When disagreement arose on the suitability of a trial for inclusion in the review or on its quality, we reached a consensus by discussion.

Randomisation method

We assessed the risk of bias from the randomisation sequence as low if this was generated using, e.g. a computer or a random numbers table; we assessed the risk of bias as unclear if the methods were not described; and we assessed the risk of bias as high if a non-random approach was used, e.g. date of birth, clinical record number.

Concealment of allocation

We assessed the risk of bias from concealment of allocation as low if neither the participants or trial investigators could foresee the allocation of the participants (e.g. using sealed opaque envelopes); we assessed the risk of bias as unclear if methods were not described; and we assessed the risk of bias as high if alternation or an open allocation schedule was used.

Blinding

We assessed the risk of bias from blinding as low if participants, investigators and outcome assessors were blinded (or if any of these were not blinded but outcome assessment was blinded and this was judged not to influence the outcome); we judged the risk of bias as unclear if this issue was not discussed; and we judged the risk of bias to be high if none of the parties involved in the trial were blinded.

Incomplete outcome data

We judged the risk of bias to be low if any withdrawals were described in full and were equal across groups; we judged the risk of bias to be unclear if insufficient information was given; and we judged the risk of bias to be high if the missing data were likely to be directly related to the outcome or if they were uneven across groups.

Measures of treatment effect

For binary outcome measures, we sought data on the number of participants with each outcome event, by allocated treated group, irrespective of compliance and whether or not the participant was later thought to be ineligible or otherwise excluded from treatment or follow-up. We aimed to calculate a pooled estimate of the treatment effect for each outcome across studies using the odds ratio (OR) (the odds of an outcome among treatment allocated participants to the corresponding odds among controls).

For continuous outcomes, we recorded either mean change from baseline for each group or mean post-treatment or intervention values and standard deviation (SD) for each group. Then, where appropriate, we planned to calculate a pooled estimate of treatment effect by calculating the mean difference (MD). If different scales had been used for the same outcome we would have considered using the standardised mean difference (SMD).

Unit of analysis issues

As we expected to find cross-over trials, we decided to analyse cross-over trials with the marginal probabilities of success method, as described by Elbourne, (Becker 1993; Elbourne 2002) rather than examining them as a parallel trial. Analysing cross-over trials in this way has been reported to avoid the problem of losing the advantage arising from cross-over trials (Elbourne 2002).

Dealing with missing data

We sought the necessary data from the original investigators if reports were incomplete. This refers particularly to the data needed to apply the marginal probabilities method to cross-over trials (Becker 1993; Elbourne 2002).

Assessment of heterogeneity

We planned to test heterogeneity between trial results using a standard Chi^2 test and the I^2 statistic using the following cut-off values (Higgins 2003):

- not important heterogeneity: 0% to 40%;
- moderate heterogeneity: 30% to 60%;
- substantial heterogeneity: 50% to 90%;
- considerable heterogeneity: 75% to 100%.

Assessment of reporting biases

We planned to assess publication bias by visual inspection of the funnel plot, and to investigate outcome reporting bias by comparing trial protocols and results from final papers, or (if protocols are not available) the methods and results sections of final papers.

Data synthesis

For the meta-analysis we planned to use a fixed-effect model unless we found moderate or significant heterogeneity, in which case we planned to use a random-effects model.

Subgroup analysis and investigation of heterogeneity

If we had identified moderate or significant heterogeneity, we planned to investigate this by subgroup analysis based on the level of the inhibitor (Hay 2000):

1. levels of 5 Bethesda units per millilitre (BU/ml) or less;
2. levels in excess of 5 BU/ml.

Sensitivity analysis

We planned to perform a sensitivity analysis based on the generation of the allocation sequence within the trials, including and excluding quasi-randomised trials.

RESULTS

Description of studies

Results of the search

A total of 15 studies were identified by the searches (Astermark 2007; Young 2008; Chuansumrit 2000; de Paula 2012; Kavakli 2006; Ljung 2013; Lusher 1998; Mahlangu 2012; NCT00108758; NCT01561391; Pruthi 2007; Santagostino 2006; Seremetis 1994; Shapiro 1998; Villar 2004) and two of these were eligible for inclusion in this review (Astermark 2007; Young 2008). The reasons for excluding the 13 studies are summarized below (Characteristics of excluded studies).

Included studies

Trial design

Both of the included trials were multicentre cross-over RCTs. One trial had two arms (Astermark 2007) and the second trial had three arms (Young 2008). For the comparison we are evaluating (rFVIIa versus aPCC) the trials were unblinded.

Participants

Participants in both trials included adults and children with severe haemophilia with inhibitors (Astermark 2007; Young 2008). The Astermark trial only included participants with haemophilia A; the Young trial included participants with both haemophilia A and B and did not separately specify the numbers of each.

The Astermark trial enrolled 66 participants; however, 14 withdrew prior to treatment or were treated only once. Diaries for a further four participants were not completed (Astermark 2007). The Young trial randomised 42 participants, with 21 completing all three treatment arms.

Interventions

Both the included trials compared rFVIIa with aPCC.

In the Young trial, rFVIIa 90 mcg/kg was given as an intravenous (IV) bolus administered at zero, three and six hours; rFVIIa 270 mcg/kg as single IV bolus (followed by two placebo infusions); and aPCC 75 IU/kg as a single IV bolus (Young 2008). Thus, participants were unblinded to the comparison between aPCC and rFVIIa, but were blinded to the dose of rFVIIa (90 mcg/kg x 3 doses versus 270 mcg/kg as a single bolus with two placebo solutions).

In the Astermark trial aPCC 75 to 100 IU/kg (target 85 IU/kg) was given as a single IV bolus; rFVIIa 90 to 120 mcg/kg (target 105 mcg/kg) was given as an IV bolus repeated after two hours (Astermark 2007). Both treatments were administered a mean time of two hours after bleeding onset.

Outcomes measured

In both the trials, due to the peculiarity of the clinical condition under evaluation, the outcomes were subjective in nature (participant judgement about the efficacy of the treatment, expressed as global evaluation, pain cessation, motility improvement, need for additional treatment). None of the outcomes measures used were common to both trials, and only one of them made assessments about the safety of the treatment (Young 2008). The primary and secondary outcomes of the Young trial were the secondary and primary outcomes of this review, respectively (Young 2008).

Excluded studies

Among the excluded trials, two were not RCTs or quasi-RCTs (Chuansumrit 2000; Seremetis 1994), five were dose-finding trials, where the comparators were not alternative therapies (Lusher 1998; Shapiro 1998; Villar 2004; Mahlangu 2012; de Paula 2012); the remaining six were randomised comparisons of different regimens of rFVIIa given to treat bleeding (Kavakli 2006; Santagostino 2006; Ljung 2013; NCT00108758) or as surgical prophylaxis (Pruthi 2007; NCT01561391).

Risk of bias in included studies

Allocation

Generation of randomisation sequence

In one trial randomisation in association with the first bleeding event was performed in a block of participants equally divided into two (Astermark 2007). The method of randomisation for that first event is not given in the paper. In the second trial, six treatment sequences were generated by the permutation of the three dosing regimens (Young 2008). The sequences were randomly assigned to the participants. There is no further information about the method of randomisation in the paper. The risk of bias has to be considered unclear in both trials due to lack of details about randomisation sequence generation; furthermore, blocking by two allows the investigator to guess the treatment assigned to the subsequent participant (Astermark 2007).

Concealment of allocation

Both trials were open label for the comparison of rFVIIa versus aPCC, which would mean there was sub-optimal allocation concealment. However, in the Young trial the comparison between the two different rFVIIa regimens did not provide details about randomisation code concealment. We therefore judged one trial to be at a high risk of bias (Astermark 2007) and one to be at an unclear risk of bias (Young 2008).

Blinding

One trial was not blinded for physicians and participants because of the major difference between the two products (physical appearance and required volume for injection); outcome assessment was also not blinded (Astermark 2007). In the second trial, participants and clinicians could not be blinded to the comparison between the two rFVIIa treatments and the aPCC treatment due to differences in physical appearance and required volume for injection, but comparison between the two rFVIIa treatments was blinded (three active boluses versus one active and two placebo boluses) (Young 2008). Outcome assessment in this trial was blinded. The risk of bias has to be considered high in both trials.

Incomplete outcome data

A total of 48 participants out of 66 completed the Astermark trial protocol for all time points (Astermark 2007). There were 14 participants who withdrew prior to treatment or were treated only once. Reasons for withdrawal included: no bleeding episodes in the study joints or the timing of prophylactic or other infusions prevented participation (six participants); lack of compliance with the protocol (three participants); concern about using a unfamiliar

product, or change of mind about participation (two participants); the trial was stopped by the Ministry of Health in one country because the products were not provided free of charge (one participant); no reason was given for the withdrawal of two participants; the diaries of four participants were not adequately completed for inclusion in the analysis. The trial was reported as to be analysed on an intention-to-treat basis, but actually appears to be analysed per protocol, we therefore assessed this trial as having a high risk of bias (Astermark 2007).

A total of 21 participants out of 42 completed the Young trial protocol (Young 2008). Fourteen participants were randomised but not treated; of the remaining 27 participants, six were withdrawn: three of these for non-compliance; two for study closure; and one because the participant moved to another centre. The trial was prematurely interrupted and analysed per protocol and thus assessed as having a high risk of bias (Young 2008).

Selective reporting

We were not able to compare the trial protocols and reports for either trial, due to unavailability of the protocols (Astermark 2007; Young 2008). No discrepancy was found between the methods and results sections of the reports. The outcomes and timing were those commonly used in the field and pre-specified as outcome measures for this review. We therefore judge there to be a low risk of bias from selective reporting.

Other potential sources of bias

Only one of the trials had an objective rather than a subjective measure as the principal outcome (Young 2008); and a risk of bias is inherent in the use of any subjective outcomes (participant-reported measures). The use of analgesics was allowed during both trials, and potentially interfered with subjective pain assessment by the participants. One trial evaluated the distribution of analgesics in the treatment groups (Astermark 2007). The remaining trial tried to adjust for the concomitant use of analgesic drugs (Young 2008). A significantly different number of knee (higher in rFVIIa-treated participants) and elbow (higher in aPCC-treated participants) bleeding events were recorded in one trial and the analysis technique used to balance for the uneven distribution of knee bleeds is unfair and not sufficiently detailed (Astermark 2007). The Young trial was interrupted by the sponsor for unspecified reasons (Young 2008).

Effects of interventions

We are unable to perform any formal meta-analyses because the two trials did not have any overlapping outcomes amenable for pooling; therefore, we have simply summarized the results of each of the trials. The authors of both trials provided the data needed to perform the marginal probabilities of success method, namely

the number of participants in each of the following groups, for all the relevant outcomes at each reported time-point: success in both treatment phases; failure in both treatment phases; success with rFVIIa; and failure with aPCC; failure with rFVIIa; and success with aPCC. As previously described by Elbourne, analysing cross-over trials in this way has been reported to avoid the problem of losing the advantage arising from cross-over trials (Becker 1993; Elbourne 2002). This is our primary analysis and results are reported in the forest plots (Data and analyses). We have also reported the outcome effect measures provided in the original trials in additional tables (Table 1; Table 2; Table 3; Table 4; Table 5).

Primary outcomes

1. Early cessation of bleeding

a. changes on any subjective or objective pain and mobility scale

The primary outcome of the Astermark trial was evaluation of haemostatic effect at six hours following treatment (Astermark 2007). An effective response was defined by creating a dichotomy of the effective and partially effective response versus poorly effective and not effective. Full details of the results analyzed with the marginal probabilities method (Becker 1993) for this outcome are presented (Analysis 1.1). A secondary outcome of the Astermark trial, not included in our protocol, is also reported in the additional tables (Table 2).

The main outcome of the Young trial was an algorithm taking into account pain and mobility scores, and it did not find any significant difference between the treatment groups (Young 2008) (Table 3; Table 4). This algorithm has not, as yet, been formally validated. The marginal probability score (Becker 1993) was recalculated separately for mobility and pain for the assessments at one, three, six and nine hours (Analysis 2.1; Analysis 2.2; Analysis 3.1; Analysis 3.2; Analysis 4.1; Analysis 4.2). The number of participants requiring analgesic drugs was not significantly different among the treatment groups (Analysis 2.3; Analysis 3.3; Analysis 4.3).

b. changes in the volume of haematoma assessed radiologically at any point in the first 48 hours

This outcome has not been assessed by either trial.

Secondary outcomes

1. Number of participants requiring additional or alternative treatment

In the Astermark trial additional doses were administered in cases where the protocol treatment regimen was not sufficient

(Astermark 2007). The timing of the additional doses varied. A small number (two) were administered within the first six hours after onset of treatment. The remainder during the balance of the 48-hour observation period (Astermark 2007).

In the Young trial, participants with an insufficient treatment response within six hours of the first treatment administration were evaluated in the clinic or by telephone to consider the use of rescue medication (Young 2008). Rescue medication was defined as additional haemostatic treatment within nine hours after the first administration of trial product. A total of eight bleeding episodes for aPCC, two for rFVIIa 270 mcg/kg and two for rFVIIa 90 mcg/kg x 3 doses required additional medication. The difference between rFVIIa 270 mcg/kg versus aPCC was statistically significant ($P = 0.032$). The efficacy difference between the aPCC treatment group and the rFVIIa 90 mcg/kg x 3 doses did not reach statistical difference ($P = 0.069$). Full details of the results about this outcome were provided in the additional tables (Table 5).

2. Number of participants with adverse effects (thromboses; allergic reactions)

The Astermark trial did not report any trial-related or drug-related adverse effects (Astermark 2007).

The Young trial did not report any thrombotic, fatal or clinical laboratory adverse events; however, it did record 32 treatment emergent adverse events in 14 participants. Of these three were in the rFVIIa 270 mcg/kg group, five were in the rFVIIa 90 mcg/kg x 3 doses group and six were in the aPCC group. None were considered to be related to the trial drug (Young 2008).

3. Correction of abnormal haemostatic laboratory test results

This outcome has not been assessed in either trial. It has to be noted that no commonly available test exists to monitor the effect of by-passing agents (both aPCC and rFVIIa).

DISCUSSION

Since the previous version of this review (Iorio 2010), 18 new potentially relevant references were found. Five trials were added to the excluded studies list and we did not find any further eligible trials. Therefore, results presented in this update continue to refer to the two trials already included in the 2010 version of this review (Iorio 2010). However, we were successful in obtaining additional data enabling us to perform the marginal probabilities analysis, although data were still not combined in a formal meta-analysis (Astermark 2007; Young 2008). The new data allowed us to report odds ratios (OR) and to take into account information provided by both treatment periods in the cross-over trials. There is no change in statistical non-significance of the results. Overall,

both the included trials showed methodological flaws. Both the treatments were shown to be effective and safe and can be used to treat bleeding in people with haemophilia with inhibitors, but were not able to prove superiority of one treatment over the other. It is to be noted that the Astermark trial was designed and analysed as an equivalence trial (Astermark 2007); the Young trial was aimed at comparing two different dosages of recombinant factor VIIa (rFVIIa) and used activated prothrombin complex concentrates (aPCC) as a reference, without pre-stating any equivalence range (Young 2008). The high number of dropouts in both trials is an important limitation. These data do not show whether the treatments were equivalent or whether one is superior to the other. Due to the widespread use in clinical practice of both by-passing agents, their efficacy was considered as already proven, and no placebo group was felt to be needed. A significant percentage of dropouts was recorded in both trials, and the Young trial was prematurely discontinued (Young 2008). We would like to highlight that we found a relevant difference in treatment efficacy independent of the drug used, i.e. aPCC or rFVIIa, among the two trials (median efficacy of 80% at six hours in the Astermark trial and 40% in the Young trial); this means that both trials showed similar effectiveness of treatment. The difference in median efficacy rates is likely to be related to the subjective nature of the outcome measures or trial protocols or both. With regards to outcome assessment, it is important to note that no objective method is fully validated as far as joint bleeding is concerned. Similarly, there is no general consensus on when assessing the anti-haemorrhagic effect. The two trials used different scales and assessment times, and in particular the Young trial used a composite algorithm to give an overall judgement of the participants response over a wide range of assessment times (Young 2008). How easily the results of the trials included in the present review can be reproduced in different contexts is hard to say.

Based on the available randomised evidence, it is not possible to consider one treatment more efficacious or safer than the other. Other systematic reviews may help in the choice of the more effective concentrates by reviewing non-randomised evidence (Lloyd Jones 2003); or by using a Bayesian approach to pool randomised and non-randomised evidence (Treur 2009); or by focusing on economical aspects (Knight 2009). Another potentially relevant issue, not considered in this systematic review, is that of viral safety of the concentrates under evaluation. The general considerations about the safety of recombinant and plasma-derived factor VIII and IX concentrates might apply also to bypassing agents

(rFVIIa and aPCC). Another aspect to be taken into account is that aPCC contains traces of factor VIII and could possibly induce an anamnestic response to be potentially avoided in patients candidate to immunotolerance treatment.

AUTHORS' CONCLUSIONS

Implications for practice

Based on the separate analysis of the two available randomised trials, rFVIIa and aPCC were found to be similar in efficacy and in causing a low risk of thromboembolic complications. Both drugs can be administered as single intravenous bolus (270 mcg/kg of rFVIIa, 75 to 100 IU/kg of aPCC). Other non-randomised evidence can be usefully taken into account in the choice of the more appropriate treatment in clinical practice. The choice between different regimens of rFVIIa is beyond the scope of this review, and should be mainly based on general considerations about the use of recombinant versus plasma-derived concentrates in specific categories of people (i.e. children).

Implications for research

There is need for further well-designed, adequately-powered randomised controlled trials to assess the relative benefits and risks of using rFVIIa compared to human plasma-derived concentrates in people with haemophilia with inhibitors. It is advisable that researchers in the field define commonly agreed objective outcome measures in order to enable easier pooling of their results thus increasing the power of comparisons. To the same, scope reporting concordant and discordant pairs in cross-over trials would be recommended. Both tasks are difficult to pursue, but very relevant and should be sought in view of the high societal costs of treating people with haemophilia with inhibitors.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Astermark 2007

Methods	Open-label cross-over multicentre RCT.
Participants	Individuals with severe haemophilia A with inhibitors not undergoing ITI. A total of 66 individuals were enrolled, but 14 withdrew prior to treatment or were treated only once. Diaries for a further 4 participants were not adequately completed Age: mean 27.5 years (range 8 - 55 years). Mean inhibitor titre 8.6 BU/ml (range 0 - 1800). 96 episodes in 48 participants.
Interventions	aPCC (FEIBA [®]) 75 - 100 IU/kg (target 85 IU/kg) as a single IV bolus. Activated rFVII (NovoSeven [®]) 90 - 120 mcg/kg (target 105 mcg/kg) as IV bolus repeated after 2 hours Both treatments were administered a mean of 2 hours after bleeding onset
Outcomes	Subjective evaluation of treatment efficacy based on a four level scale (effective, partially effective, poorly effective, not effective); efficacy was defined as effective or partially effective by participant rating at 6 hours (primary) and at various times from 2 - 48 hours (secondary) Subjective evaluation of stop of bleeding (binary outcome). Additional treatments and the occurrence of re-bleeding were recorded
Notes	Use of analgesics was allowed and its distribution in the treatment group was evaluated A significantly different number of knee (higher in NovoSeven [®] -treated participants) and elbow (higher in aPCC-treated participants) bleeding events were recorded. The analysis technique used to balance for the uneven distribution of knee bleeds is unclear and not sufficiently detailed

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation in association with the first bleeding event was performed in a block of participants equally divided into two
Allocation concealment (selection bias)	High risk	Open-label trial. A randomisation list specifying the order of treatment for enrolled participants was provided to each participating centre
Blinding (performance bias and detection bias) All outcomes	High risk	Blinding was not possible for physicians and participants because of difference between the 2 products (physical appearance and required volume for injection). Outcome as-

Astermark 2007 (Continued)

		essment was not blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	The trial was analysed on a per protocol basis.
Selective reporting (reporting bias)	Low risk	Outcome data reported in the methods and the results sections correspond
Other bias	High risk	Use of analgesics allowed during the trial. A significantly different number of knee (higher in participants treated with Novo-seven®) and elbow (higher in participants treated with aPCC) bleeding events were recorded. The analysis technique used to balance for the uneven distribution of knee bleeds is unclear and not sufficiently detailed

Young 2008

Methods	Open-label cross-over multicentre 3-tier RCT. The comparison between rFVIIa and aPCC was open label, while the comparison between the two different rFVIIa regimens was concealed Outcome assessor was blinded.	
Participants	Individuals with severe haemophilia A and B with inhibitor (the number of participants with A and B was not separately specified). A total of 42 were randomised, with 21 completing all 3 arms of treatment Age: mean 19.5 years (range 1 - 54 years).	
Interventions	Activated rrF VII (NovoSeven®) 90 mcg/kg as IV bolus administered at 0, 3 and 6 hours. Activated recombinant factor VII (NovoSeven®) 270 mcg/kg as single IV bolus (followed by 2 placebo infusions) aPCC (FEIBA®) 75 IU/kg as a single IV bolus.	
Outcomes	Primary outcomes Number of participants requiring additional treatment. Secondary outcomes Subjective pain and mobility scale rating evaluated as global treatment response (composite end-point) and separately Rate of adverse events.	
Notes	The trial states that the analysis was performed on an intention-to-treat basis, but the data seems to have been analysed on-treatment	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement

Young 2008 (Continued)

Random sequence generation (selection bias)	Unclear risk	6 treatment sequences were generated by the permutation of the 3 dosing regimens. The sequences were randomly assigned to the participants
Allocation concealment (selection bias)	Unclear risk	The comparison between rFVIIa and aPCC was open label, while the comparison between the 2 different rFVIIa regimens was described as blinded without details about randomisation code concealment
Blinding (performance bias and detection bias) All outcomes	High risk	Participants and clinicians could not be blinded to comparison between both NovoSeven® treatments and the FEIBA® treatment due to differences in physical appearance and required volume for injection, but comparison of 2 NovoSeven® treatments was blinded (3 active versus 1 active and 2 placebo doses). Outcome assessment was blinded for the treatments
Incomplete outcome data (attrition bias) All outcomes	High risk	The trial states that the analysis was performed on an intention-to-treat basis, but the data seems to have been analysed on-treatment
Selective reporting (reporting bias)	Low risk	Outcome data reported in the methods and results sections correspond
Other bias	Unclear risk	Use of analgesics allowed during the trial. Distribution of analgesics use among group was evaluated The trial was interrupted by the sponsor for unspecified reasons

aPCC: activated prothrombin complex concentrates

BU: Bethesda units

ITI: immune tolerance induction

IV: intravenous

RCT: randomised controlled trial

rFVIIa: recombinant factor VIIa

vs: versus

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Chuansumrit 2000	Not a randomised or quasi-randomised controlled trial. Prospective, open-label, uncontrolled, observational study.
de Paula 2012	Dosage-finding trial: comparator is not an alternative therapy
Kavakli 2006	Double-blind cross-over RCT comparing two different regimens of rFVIIa
Ljung 2013	RCT comparing two different regimens of rFVIIa.
Lusher 1998	Dosage-finding trial: comparator is not an alternative therapy. Double-blind RCT.
Mahlangu 2012	Dosage-finding trial: comparator is not an alternative therapy
NCT00108758	RCT comparing two different regimens of rFVIIa.
NCT01561391	RCT comparing two different regimens of rFVIIa.
Pruthi 2007	Open label randomised RCT comparing two different regimens of rFVIIa (90 mcg/kg boluses versus continuous infusion) in people with haemophilia undergoing major surgery
Santagostino 2006	Open label cross-over RCT comparing two different regimens of rFVIIa
Seremetis 1994	Not a randomised or quasi-randomised controlled trial. Phase II safety and efficacy trial.
Shapiro 1998	Dosage-finding trial: comparator is not an alternative therapy. Double-blind RCT.
Villar 2004	Dosage-finding trial: comparator is not an alternative therapy

RCT: randomised controlled trial

rFVIIa: recombinant factor VIIa

DATA AND ANALYSES

Comparison 1. aPCC 75 - 100 IU/kg vs rFVIIa 90 - 120 mcg/kg x 2 doses

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Treatment efficacy judgement	1		Odds Ratio (Fixed, 95% CI)	Totals not selected
1.1 At 2 hours	1		Odds Ratio (Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 At 6 hours	1		Odds Ratio (Fixed, 95% CI)	0.0 [0.0, 0.0]
1.3 At 12 hours	1		Odds Ratio (Fixed, 95% CI)	0.0 [0.0, 0.0]
1.4 At 24 hours	1		Odds Ratio (Fixed, 95% CI)	0.0 [0.0, 0.0]
1.5 At 36 hours	1		Odds Ratio (Fixed, 95% CI)	0.0 [0.0, 0.0]
1.6 At 48 hours	1		Odds Ratio (Fixed, 95% CI)	0.0 [0.0, 0.0]

Comparison 2. rFVIIa 270 ug/kg vs rFVIIa 90 ug/kg x 3 doses

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mobility evaluation	1		Odds Ratio (Fixed, 95% CI)	Totals not selected
1.1 At 1 hour	1		Odds Ratio (Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 At 3 hours	1		Odds Ratio (Fixed, 95% CI)	0.0 [0.0, 0.0]
1.3 At 6 hours	1		Odds Ratio (Fixed, 95% CI)	0.0 [0.0, 0.0]
1.4 At 9 hours	1		Odds Ratio (Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Pain evaluation	1		Odds Ratio (Fixed, 95% CI)	Totals not selected
2.1 At 1 hour	1		Odds Ratio (Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 At 3 hours	1		Odds Ratio (Fixed, 95% CI)	0.0 [0.0, 0.0]
2.3 At 6 hours	1		Odds Ratio (Fixed, 95% CI)	0.0 [0.0, 0.0]
2.4 At 9 hours	1		Odds Ratio (Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Need for rescue medication	1		Odds Ratio (Fixed, 95% CI)	Totals not selected

Comparison 3. rFVIIa 270 ug/kg vs APCC 75 U/kg

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mobility evaluation	1		Odds Ratio (Fixed, 95% CI)	Totals not selected
1.1 At 6 hours	1		Odds Ratio (Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 At 9 hours	1		Odds Ratio (Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Pain evaluation	1		Odds Ratio (Fixed, 95% CI)	Totals not selected
2.1 At 1 hour	1		Odds Ratio (Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 At 3 hours	1		Odds Ratio (Fixed, 95% CI)	0.0 [0.0, 0.0]
2.3 At 6 hours	1		Odds Ratio (Fixed, 95% CI)	0.0 [0.0, 0.0]
2.4 At 9 hours	1		Odds Ratio (Fixed, 95% CI)	0.0 [0.0, 0.0]

3 Need for rescue medication	1	Odds Ratio (Fixed, 95% CI)	Totals not selected
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Comparison 4. rFVIIa 90 ug/kg x 3 doses vs APCC 75 U/kg

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mobility evaluation	1		Odds Ratio (Fixed, 95% CI)	Totals not selected
1.1 At 6 hours	1		Odds Ratio (Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 At 9 hours	1		Odds Ratio (Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Pain evaluation	1		Odds Ratio (Fixed, 95% CI)	Totals not selected
2.1 At 1 hour	1		Odds Ratio (Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 At 3 hours	1		Odds Ratio (Fixed, 95% CI)	0.0 [0.0, 0.0]
2.3 At 6 hours	1		Odds Ratio (Fixed, 95% CI)	0.0 [0.0, 0.0]
2.4 At 9 hours	1		Odds Ratio (Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Need for rescue medication	1		Odds Ratio (Fixed, 95% CI)	Totals not selected

ADDITIONAL TABLES

Table 1. aPCC 75-100 IU/kg vs rFVIIa 90 - 120 mcg/kg x 2 doses - Treatment efficacy judgement

Study ID	Hours (pts number)	aPCC n (%)	rFVIIa n (%)	90% CI of the difference (%)	P value
Astermark 2007	2 (48)	36 (75.0)	29 (60.4)	-0.73 to 29.9	0.482
	6 (47)	38 (80.9)	37 (78.7)	-11.42 to 15.67	0.059
	12 (45)	38 (80.0)	38 (84.4)	-18.08 to 9.19	0.101
	24 (42)	40 (95.2)	36 (85.7)	-1.29 to 20.33	0.202
	36 (41)	41 (100)	37 (90.2)	2.13 to 17.38	0.129
	48 (41)	40 (97.6)	35 (85.4)	2.05 to 22.34	0.325

The table reports the number and % of participants who judged the treatment efficacious for any treatment and any time point. The 90% CIs of the difference test the hypothesis of equivalence between the treatments. When considering the difference at 2 hours, it has to be taken into account that this time point is before the administration of the second rFVIIa bolus.

aPCC: activated prothrombin complex concentrates

CI: confidence interval

rFVIIa: recombinant factor VIIa

Table 2. aPCC 75 - 100 IU/kg vs rFVIIa 90 - 120 mcg/kg x 2 doses - Bleeding stop

Study ID	Hours (number of participants)	aPCC (%)	rFVIIa (%)	90% CI of the difference (%)	P value
Astermark 2007	2 (47)	53.2	38.3	0.06 to 29.72	0.495
	6 (46)	76.1	65.2	-2.73 to 24.47	0.309
	12 (45)	77.8	75.6	-11.92 to 16.37	0.069
	24 (42)	90.5	85.7	-4.75 to 14.28	0.038
	36 (41)	95.1	87.8	-1.45 to 16.09	0.075
	48 (41)	95.1	92.7	4.48 to 9.36	0.001

The table reports the number and % of participants who judged the treatment efficacious for any treatment and any time point. The 90% CIs of the difference test the hypothesis of equivalence between the treatments. When considering the difference at 2 hours, it has to be taken into account that this time point is before the administration of the second rFVIIa bolus.

aPCC: activated prothrombin complex concentrates

CI: confidence interval

rFVIIa: recombinant factor VIIa

Table 3. aPCC 75 IU/kg vs rFVIIa 270 mcg/kg vs rFVIIa 90 mcg/kg x 3 doses - Pain scale

Study ID	Outcome	rFVIIa 270 mcg/kg (N = 24)	rFVIIa 90 mcg/kg x 3 (n = 22)	aPCC 75 IU/kg (n = 22)
Young 2008	Positive treatment response (%)	45.8	54.5	27.3

The response was globally evaluated 9 hours after treatment. The positive response were defined as at least 3 positive assessments at 1, 3, 6 and 9 hours. The positive assessment was defined on the base of a 3-level scale (more pain, no difference, less pain). There were no statistically significant differences between treatments (P = 0.219).

aPCC: activated prothrombin complex concentrates

rFVIIa: recombinant factor VIIa

Table 4. aPCC 75 IU/kg vs rFVIIa 270 mcg/kg vs rFVIIa 90 mcg/kg x 3 doses - Mobility scale

Study ID	Outcome	rFVIIa 270 mcg/kg (N = 24)	rFVIIa 90 mcg/kg x 3 (n = 22)	aPCC 75 IU/kg (n = 22)
Young 2008	Positive treatment response (%)	25.0	45.5	22.7

The response was globally evaluated 9 hours after treatment. The positive response were defined as at least 3 positive assessments at 1, 3, 6 and 9 hours. The positive assessment was defined on the base of a 3-level scale (more mobility, no difference, less mobility).

There were no statistically significant differences between treatments (P = 0.903).

aPCC: activated prothrombin complex concentrates

rFVIIa: recombinant factor VIIa

Table 5. aPCC 75 IU/kg vs rFVIIa 270 mcg/kg vs rFVIIa 90 mcg/kg x 3 doses - Rescue medication use

Study ID	Outcome	rFVIIa 270 mcg/kg (n = 24)	rFVIIa 90 mcg/kg x 3 (n = 22)	aPCC 75 IU/kg (n = 22)
Young 2008	Participants requiring rescue medication n (%)	2 (8.3)	2 (9.1)	8 (36.4)

Participants with an insufficient treatment response within 6 hours of the first treatment administration were evaluated in the clinic or by phone to consider the use of rescue medication. Rescue medication was defined as additional haemostatic treatment within 9 hours post first administration of trial product. The difference between rFVIIa 270 mcg/kg vs aPCC was statistically significant (P = 0.032). The efficacy difference between the aPCC treatment group and the rFVIIa 90 x 3 mcg/kg did not reach statistical difference (P = 0.069).

aPCC: activated prothrombin complex concentrates

rFVIIa: recombinant factor VIIa

WHAT'S NEW

Last assessed as up-to-date: 16 October 2015.

Date	Event	Description
16 October 2015	New citation required but conclusions have not changed	While no new trials have been included in the update, after receiving additional data from trial authors, the two included (cross-over) trials were re-analyzed using the marginal probabilities method (Becker 1993; Elbourne 2002).
16 October 2015	New search has been performed	Literature searches were performed and the manuscript was updated

HISTORY

Protocol first published: Issue 4, 2003

Review first published: Issue 2, 2004

Date	Event	Description
15 February 2011	Amended	Contact details updated.
7 July 2010	New search has been performed	The search of the Group's Coagulopathies Trials Register identified six references to five new trials; two trials have been included (Astermark 2007; Young 2008) and the remaining three trials have been excluded (Kavakli 2006; Pruthi 2007; Santagostino 2006). The review protocol was modified to include people with both haemophilia A and haemophilia B. No difference exists in the treatment of individuals with inhibitors in each of the two conditions. We therefore see no reason to limit the review to individuals with haemophilia A, even if most of the people with inhibitors are haemophilia A patients (inhibitor occurrence in haemophilia B is much more rare)
7 July 2010	New citation required and conclusions have changed	A new review team has taken on this review and updated it including two new trials where previously none were included
14 November 2008	Amended	Converted to new review format.
15 February 2006	New search has been performed	The search of the Group's Coagulopathies Trials Register identified one reference (Villar 2004), this has now been listed under 'Excluded studies'
11 February 2005	New search has been performed	The search of the Group's Coagulopathies Trials Register identified one trial, but this was not eligible for inclusion in the review
24 February 2004	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Contributions to the current update:

DM is the lead reviewer and guarantor of the review.

AI and DM screened the search results, screened retrieved papers against inclusion criteria and entered data into RevMan.

KD performed the statistical analysis

DM, AI, and MM drafted the update of the review

MM and AI provided a clinical perspective.

Contributions for Issue 8, 2010

AI is the lead reviewer and guarantor of the review.

AI and DM screened the search results, screened retrieved papers against inclusion criteria and entered data into RevMan.

AI, DM and MM drafted the update of the review

MM provided a clinical perspective.

Review up to Issue 2, 2006

DH was the guarantor of the review.

DH coordinated the review.

DH, MLJ and MM drafted the title.

DH and MM drafted the protocol.

DH and MLJ screened the search results.

DH organised the retrieval of papers.

DH and MLJ screened retrieved papers against inclusion criteria.

DH entered data into RevMan.

DH, SP and MLJ provided a methodological perspective.

MM provided a clinical perspective.

DH and MLJ wrote the review.

SP secured funding for the review.

SP, MLJ, Chris Knight and Jeremy Wight and Elizabeth Currie performed previous work that was the foundation of current study.

DECLARATIONS OF INTEREST

Davide Matino declares no conflict of interest.

Michael Makris has received fees for consultancy and sponsorship to attend scientific meetings from Baxter Healthcare and NovoNordisk.

Kerry Dwan declares no conflict of interest.

Roberto D'Amico declares no conflict of interest.

Alfonso Iorio has acted as paid lecturer and has been reimbursed for participation at International Congresses by both NovoNordisk and Baxter Healthcare.

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Internal sources

- No sources of support supplied

External sources

- National Institute for Health Research, UK.

This systematic review was supported by the National Institute for Health Research, via Cochrane Infrastructure funding to the Cochrane Cystic Fibrosis and Genetic Disorders Group.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The review protocol was modified to include people with haemophilia A and haemophilia B, since no difference exists in the treatment of individuals with inhibitor in the two conditions. Even if most of the individuals with inhibitors are people with haemophilia A (inhibitor occurrence in haemophilia B is much more rare), there is no reason to limit the review to haemophilia A.

NOTES

The current review was originally based on a previous systematic review of the management of inhibitors in haemophilia A funded by the London NHS Directorate of Health and Social Care:

Wight J, Lloyd Jones M, Knight C, Paisley S, Currie E. The management of inhibitors in haemophilia A: a systematic review and economic model. London: London NHS Directorate of Health and Social Care, 2002.

Paisley S, Wight J, Currie E, Knight C. The management of inhibitors in haemophilia A: introduction and systematic review of current practice. *Haemophilia*. 2003;9:405-417

Wight J, Paisley S. The epidemiology of inhibitors in haemophilia A: a systematic review. *Haemophilia*. 2003;9:418-435.

Wight J, Paisley S, Knight C. Immune tolerance induction in patients with haemophilia A with inhibitors: a systematic review. *Haemophilia*. 2003;9:436-463.

Lloyd Jones M, Wight J, Paisley S, Knight C. Control of bleeding in patients with haemophilia A with inhibitors: a systematic review. *Haemophilia*. 2003;9:464-520.

Knight C, Paisley S, Wight J, Jones ML. Economic modelling of different treatment strategies for haemophilia A with high responding inhibitors. *Haemophilia*. 2003;9:521-540.

INDEX TERMS

Medical Subject Headings (MeSH)

Acute Disease; Blood Coagulation Factors [* therapeutic use]; Factor VIII [immunology; therapeutic use]; Factor VIIa [* therapeutic use]; Hemophilia A [blood; * drug therapy]; Hemophilia B [blood; * drug therapy]; Hemorrhage [* drug therapy]; Randomized Controlled Trials as Topic; Recombinant Proteins [therapeutic use]

MeSH check words

Humans