2.11 Haemostatics

Eptacog alfa (recombinant factor VIIa: rFVIIa)

รูปแบบ sterile powder 1.2 mg/vial

ชะลอการพิจารณา เหตุผล ยังไม่มีข้อมูลด้านความคุ้มค่าทางเศรษฐศาสตร์

1. ข้อมูลโดยสรุป

ประสิทธิภาพในแต่ละข้อบ่งใช้ที่เสนอ

พบว่า rFVIIa มีประสิทธิภาพในผู้ป่วยฮีโมฟีเลียเอหรือบีหรือผู้ป่วยที่ขาด factor VIIa โดยกำเนิด[1] และในการศึกษาที่เป็นเชิงเปรียบเทียบพบว่า rFVIIa มีประสิทธิภาพไม่ด้อยไปกว่า activated prothrombin complex concentrate[2-5] หรือ factor VIII concentrate[6-8] สำหรับข้อมูลในผู้ป่วย Glanzmann's thrombasthenia มีข้อมูลในลักษณะ case reports เท่านั้น[9]

ข้อมูลด้านความปลอดภัย

ไม่มีข้อน่ากังวลด้านความปลอดภัยหากใช้ในผู้ป่วยฮีโมฟีเลีย หรือตามข้อบ่งใช้ที่ได้รับอนุมัติ การใช้ rFVIIa นอกข้อบ่งใช้ที่ได้รับอนุมัติ (off-label use) มีผลให้เกิด thromboembolic events มากขึ้น[10, 11]

ข้อมูลด้านรายการยาและการเบิกจ่ายในต่างประเทศ

ไม่พบข้อมูล rFVIIa ในรายการยาขององค์การอนามัยโลก[12-14] สก็อตแลนด์[15] และออสเตรเลีย[16] อย่างไรก็ตาม ประเทศออสเตรเลียมีหน่วยงานสำหรับบริหารจัดการ coagulating factors โดยเฉพาะ[17, 18]

ข้อมูลด้านราคา และการจัดหาผลิตภัณฑ์

ราคาของ rFVIIa sterile powder 1.2 mg/vial ที่เสนอให้พิจารณาไว้ในบัญชียาหลักแห่งชาติ รอบปี 2553 – 2555 ขวดละ 26,750 บาท โดยมีปริมาณการผลิตหรือนำเข้าในปี 2552 ทั้งสิ้น 4,160 ขวด

จากราคาดังกล่าว คาดการณ์ค่าใช้จ่ายต่อผู้ป่วย 1 ราย ต่อการรักษาเลือดออก 1 ครั้ง ประมาณ **46,812 - 160,500** บาท (คำนวณโดยให้ยาครั้งละ 35 to 120 µg/kg และน้ำหนักผู้ป่วยเฉลี่ย 60 kg)[1]

ข้อมูลด้านความคุ้มค่าทางเศรษฐศาสตร์

ข้อมูลด้านการศึกษาในต่างประเทศ พบว่าการใช้ rFVIIa ในผู้ป่วยฮีโมฟีเลียระดับอ่อน-ปานกลาง (mild-moderate) และระดับ ปานกลาง-รุนแรง (moderate-severe) ประหยัดค่าใช้จ่ายมากกว่าการใช้ activated prothrombin complex concentrate[4, 19, 20] หรือ factor VIII concentrate[21] ส่วนการใช้ในผู้ป่วยฮีโมฟีเลียระดับอ่อนมีค่าใช้จ่ายสูงกว่า activated prothrombin complex concentrate[22]

ยังไม่มีข้อมูลศึกษาด้านความคุ้มค่าทางเศรษฐศาสตร์ของยา rFVIIa ในประเทศไทย

2. แนวทางการจัดทำข้อมูล

rFVIIa เป็นยาที่ภาคเอกชนเสนอเพื่อให้พิจารณาเป็นบัญชียาหลักแห่งชาติ โดยมีข้อบ่งใช้ที่เสนอดังนี้

เงื่อนไขที่เสนอ

ใช้ในผู้ป่วยที่มีภาวะเลือดออกรุนแรงซึ่งอาจมีอันตรายถึงแก่ชีวิตหรือกรณีเตรียมผู้ป่วยก่อนผ่าตัดใหญ่ และมีข้อใดข้อหนึ่งดังต่อไปนี้

1) ผู้ป่วยฮีโมฟีเลียที่เกิดจากพันธุกรรม (congenital haemophilia) ที่มีสารต่อต้าน (inhibitors) ต่อ coagulation factors VIII หรือ IX
2) ผู้ป่วยฮีโมฟิเลียที่เกิดขึ้นภายหลัง (acquired haemophilia) ที่ไม่ตอบสนองต่อการรักษาด้วยยากดภูมิคุ้มกัน
3) ผู้ป่วยที่ขาด Factor VII แต่กำเนิด
4) ผู้ป่วย Glanzmann's thrombasthenia ที่มีภูมิต้านทานต่อ GP IIb-IIIa และ/หรือ HLA และมีประวัติหรือกำลังอยู่ในภาวะไม่ตอบสนองต่อการให้เกร็ดเลือด

ฝ่ายเลขานุการฯ ได้สืบค้นข้อมูลจากฐานข้อมูลต่างๆ โดยใช้ชื่อยา recombinant factor VIIa เป็นคำสำคัญ และคัดเลือกผลลัพธ์เฉพาะที่เกี่ยวข้องกับข้อบ่งใช้ซึ่งเสนอให้พิจารณา

3. รายละเอียดข้อมูลเชิงวิชาการ

3.1 ข้อมูลจากรายการยาในต่างประเทศ

3.1.1 ข้อมูลจาก WHO Model Formulary 2008[12]

ไม่พบข้อมูล recombinant factor VIIa พบเฉพาะข้อมูล factor VIII concentrate และ factor IX (coagulation factors II, VII, IX, X) concentrate

3.1.2 ข้อมูลจาก WHO Model Formulary for Children 2010[13]

ไม่พบข้อมูล recombinant factor VIIa พบเฉพาะข้อมูล factor VIII concentrate และ factor IX (coagulation factors II, VII, IX, X) concentrate

3.1.3 ข้อมูลจาก WHO Model Lists 2011[14]

ไม่พบข้อมูล recombinant factor VIIa พบเฉพาะข้อมูล factor VIII concentrate และ factor IX (coagulation factors II, VII, IX, X) concentrate

3.1.4 ข้อมูลจาก Australian Pharmaceutical Benefit Scheme 2011, May[16]

ไม่มีข้อมูลที่กล่าวถึง coagulation factors และไม่ได้กล่าวถึงโรค haemophilia

สำหรับการบริหารจัดการเวชภัณฑ์เลือดและที่เกี่ยวกับเลือด มีหน่วยงานรับผิดชอบโดยตรงคือ National Blood Authority ภายใต้หน่วยงาน Health and Aeging ซึ่งในปี 2009 – 2010 ได้รับงบประมาณจัดซื้อ rFVIIa 26.42 ล้านเหรียญออสเตรเลีย[17, 18]

The National Blood Authority, an Australian Government agency within the Health and Ageing portfolio, is responsible for contributing to ensuring the adequate, safe, secure and affordable supply of blood and blood related products.

The *National Blood Authority Act 2003* and the National Blood Agreement outline the role of the NBA. The NBA:

- works with jurisdictions to determine the clinical requirements for blood and blood products to meet national needs, and develops an annual supply plan and budget
- negotiates and manages national contracts with suppliers of blood and blood products to obtain the products needed
- assesses blood supply risk and engages in contingency planning for risks arising in the sector and impacting on the sector
- supports the work of the jurisdictions to improve the way blood products are used—including by developing and facilitating strategies and programs that will improve the safety, quality and effectiveness of blood usage, particularly in the areas of national standards, guidelines and data provision
- provides expert advice to support government policy development, including on identification of emerging risks, developments, trends and new opportunities
- manages the evaluation of proposals for blood sector improvements, including proposals for new products, technologies and system change
- provides secretariat support to the Jurisdictional Blood Committee.

[http://www.nba.gov.au/publications/0910report/chapter01/1.4.html]

The 2009–10 budget approved by health ministers for the supply and management of blood and blood related products and services was $910.8 million, of which $456.1 million was for fresh blood products and plasma collection and $426.9 million for plasma and recombinant products. Figure 3.1 shows the allocation of this funding to each product category. The list of products the NBA purchased from suppliers to meet this demand is provided in Table 3.1.

Novo Nordisk Pharmaceuticals Pty Ltd --- Imported Blood Products → Recombinant Factor VIIa --- 2009–10 ($m) 26.42

ในเว็บไซต์ของ TGA มีข้อมูลเกี่ยวกับ rFVIIa เป็นยากำพร้า

Orphan drugs

http://www.tga.gov.au/industry/pm-orphan-drugs.htm

Drug: eptacog alfa (NovoSeven)

Sponsor: Novo Nordisk Pharmaceuticals Pty Ltd

Date of designation: 14 January 2005

Indication: for the prevention and treatment of bleeding episodes in patients with congenital Factor VII deficiency or Glanzmann's Thrombasthenia.

Drug: NOVOSEVEN brand of eptacog alfa (activated) bhk

Sponsor: Novo Nordisk Pharmaceuticals Pty Ltd

Date of designation: 30 January 2007

Indication: for the treatment of postpartum haemorrhage in patients unresponsive to standard obstetrical management, oxytocic drugs and standard blood component therapy prior to major invasive therapy

Dose: powder for injection [http://www.nba.gov.au/publications/0910report/chapter03/3.1.html]

3.1.5 ข้อมูลจาก Lothian Joint Formulary 2011[15]

ไม่มีข้อมูลที่เกี่ยวกับ coagulating factors

3.2 ข้อมูลจาก drug monographs

3.2.1 ข้อมูลจาก MicroMedex 2011[1]

ตารางที่ 2 ข้อมูลการประเมินโดย MicroMedex 2011

Evaluation	Bleeding - Hemophilia, with inhibitors to Factor VIII or Factor IX		Acquired factor VIII deficiency disease - Bleeding		Bleeding - Factor VII deficiency		Glanzmann's thrombasthenia	
	Adult	*Pediatric*	*Adult*	*Pediatric*	*Adult*	*Pediatric*	*Adult*	*Pediatric*
US FDA Approval	Yes	Yes	Yes	Yes	Yes	Yes	No	No
Efficacy	E	E	F	F	E	F	F	F
Recommendation	I	I	IIa	IIa	IIa	IIa	IIb	IIb
Strength of evidence	B	B	B	B	B	B	C	C

หมายเหตุ: ตัวย่อ US FDA approval = การอนุมัติข้อบ่งใช้โดยองค์การอาหารและยาสหรัฐอเมริกา, yr = years, mo = months; *MicroMedex efficacy* ตัวย่อ E = effective, F = evidence favors efficacy, I = evidence is inconclusive, X = ineffective; *MicroMedex recommendations class* แบ่งเป็น I, IIa, IIb, III, และ indeterminant ซึ่ง I = การใช้ยาเป็นประโยชน์และควรให้ผู้ป่วยใช้, IIa = ผู้ป่วยส่วนมากได้รับประโยชน์จากการใช้ยา, IIb = ผู้ป่วยอาจได้รับประโยชน์จากการใช้ยา จึงแนะนำให้พิจารณาในบางกรณี, III = การใช้ยาไม่มีประโยชน์ ควรหลีกเลี่ยง, indeterminant = ไม่สามารถสรุปได้จากหลักฐานที่มี; *MicroMedex strength of evidence* แบ่งเป็น category A, B, C, no evidence ซึ่ง A = มีหลักฐานที่เป็น meta-analysis จาก randomized-controlled trial (RCT) ซึ่งเป็นไปในทางเดียวกัน หรือ RCT ที่ดี หรือที่มีผู้เข้าร่วมการทดลองจำนวนมาก, B = มีหลักฐานที่เป็น meta-analysis จาก RCT ซึ่งขัดแย้งกัน มี RCT ที่มีผู้เข้าร่วมการทดลองน้อย ออกแบบการทดลองไม่ดี หรือไม่ใช่การทดลองแบบ RCT, C = เป็น expert's opinion, case reports, หรือ case series

3.3 ข้อมูลจาก practice guidelines และการทบทวนวรรณกรรม

3.3.1 ข้อมูลจาก uptodate online 19.1

Hoffman 2011[23] กล่าวถึง ประโยชน์ในการใช้ rFVIIa ไว้ดังนี้

ข้อบ่งใช้ที่ได้รับการขึ้นทะเบียน ทั้งในอเมริกาและยุโรป ได้แก่ ผู้ป่วยฮีโมฟีเลียเอและบีที่มีสารต้าน factor VIII หรือ IX ตามลำดับ และใช้ในผู้ป่วยที่ขาด factor VII โดยกำเนิด

US FDA ยังอนุมัติข้อบ่งใช้ในผู้ป่วยที่เป็น acquired haemophilia

ส่วนยุโรปอนุมัติเพิ่มในข้อบ่งใช้ Glanzmann's thrombasthenia

CLINICAL UTILITY

Approved indications — The United States Food and Drug Administration (FDA)-approved indications for rFVIIa include:

- Treatment or prevention of bleeding in patients with hemophilia A or B who have inhibitors to factors VIII or IX, respectively
- Treatment or prevention of bleeding episodes in patients with acquired hemophilia
- Treatment or prevention of bleeding episodes in patients with congenital factor VII deficiency

This product is currently licensed in Europe for bypassing inhibitors to factors VIII and IX in patients with hemophilia A and B, as well as for treatment of congenital factor VII deficiency and Glanzmann's thrombasthenia [40]. While the efficacy of rFVIIa for these conditions is well established, the optimal dosing regimens are not.

3.3.2 ข้อมูลจาก NICE guidance[24]

ไม่พบข้อมูลที่เกี่ยวข้อง

3.3.3 ข้อมูลจาก NHS evidence[25]

ดูหัวข้อหลักฐานเชิงประจักษ์ 4. ข้อย่อย 4.3

3.3.4 ข้อมูลจาก practice guidelines ซึ่งสืบค้นจาก Pubmed

จากการสืบค้นฐานข้อมูล Pubmed ด้วยคำสำคัญ ("Factor VIIa"[Mesh] OR "recombinant FVIIa" [Supplementary Concept]) AND "Practice Guideline" [Publication Type] เมื่อวันที่ 4 กรกฎาคม 2554 พบทั้งหมด 6 ผลลัพธ์ ไม่พบผลลัพธ์ที่เกี่ยวข้องโดยตรง

3.4 ข้อมูลจากหลักฐานเชิงประจักษ์

3.4.1 Cochrane Library

พบข้อมูลที่เกี่ยวข้อง 3 ผลลัพธ์ โดยในเรื่องที่ 1 คือการรักษาผู้ป่วยฮีโมฟีเลียที่มีสารต้านด้วย rFVIIa เปรียบเทียบกับ activated prothrombin complex concentrate แม้ว่าคุณภาพของการศึกษายังไม่ดีนัก แต่ก็พอจะสรุปได้ว่ายาทั้งสองมีประสิทธิภาพไม่ต่างกัน[2]

ส่วนอีก 2 การศึกษาเป็นการศึกษาเพื่อดูผลของการใช้ยาแบบป้องกัน และการศึกษาในผู้ป่วยที่ไม่ได้เป็นฮีโมฟีเลีย ซึ่งไม่ใช่ข้อสนใจในการทบทวนวรรณกรรมในครั้งนี้[26, 27]

Iori, et al., 2010

Main results

A total of ten trials were identified, two of which (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 (rFVIIa and aPCC appeared to have a similar haemostatic effect in both studies, without increasing thromboembolic risk.

Authors' conclusions

Although the main conclusion should be the need for further randomised controlled trials, we conclude that both rFVIIa and aPCC can be used to treat bleeding in haemophiliacs with inhibitors.

Stobart, et al., 2006

Main results

Twenty-nine studies were identified; four studies (including 37 participants) were eligible for inclusion. Three studies evaluated

hemophilia A; one showed a decrease in frequency of joint bleeds with prophylaxis compared to placebo (non-physiological dose), with a rate difference (RD) -10.80 (95% confidence interval (CI) -16.33 to -5.27) bleeds per year. The remaining two studies evaluating hemophilia A compared two prophylaxis regimens, one study showed no difference in joint bleed frequency, RD -5.04 (95%CI -17.02 to 6.94) bleeds per year and another failed to demonstrate an advantage of factor VIII dosing based on individual pharmacokinetic data over the standard prophylaxis regimen with RD -0.14 (95% CI -1.34 to 1.05) bleeds per year. The fourth study evaluated hemophilia B and showed fewer joint bleeds with weekly (15 IU/kg) versus bi-weekly (7.5 IU/kg) prophylaxis, RD -3.30 (95% CI -5.50 to - 1.10) bleeds per year.

Authors' conclusions

There is insufficient evidence from randomised controlled trials to determine whether prophylactic clotting factor concentrates decrease bleeding and bleeding-related complications in hemophilia A or B, compared to placebo, on-demand treatment, or prophylaxis based on pharmacokinetic data from individuals. Well-designed RCTs are needed to assess the effectiveness of prophylactic clotting factor concentrates. Two clinical trials are ongoing.

Lin, et al., 2011

Main results

Twenty-five RCTs were included: 24 were placebo-controlled double-blind RCTs and one compared different doses of rFVIIa.

Fourteen trials involving 1137 participants examined the prophylactic use of rFVIIa; 713 received rFVIIa. There was no evidence of mortality benefit (RR 1.06; 95% CI 0.50 to 2.24). There was decreased blood loss (WMD -272 mL; 95% CI -399 to -146) and decreased red cell transfusion requirements (WMD -243 mL; 95% CI -393 to -92) with rFVIIa treatment; however these values were likely overestimated due to the inability to incorporate data from trials showing no difference of rFVIIa treatment compared to placebo. There was a trend in favour of rFVIIa in the number of participants transfused (RR 0.91; 95% CI 0.82 to 1.02). But there was a trend against rFVIIa with respect to thromboembolic adverse events (RR 1.32; 95% CI 0.84 to 2.06).

Eleven trials involving 2366 participants examined the therapeutic use of rFVIIa; 1507 received rFVIIa. There were no outcomes where any observed advantage, or disadvantage, of rFVIIa over placebo could not have been observed by chance alone. There was a trend in favour of rFVIIa for reducing mortality (RR 0.89; 95% CI 0.77 to 1.03). However, there was a trend against rFVIIa for increased thromboembolic adverse events (RR 1.21; 95% CI 0.93 to 1.58).

Authors' conclusions

The effectiveness of rFVIIa as a more general haemostatic drug, either prophylactically or therapeutically, remains unproven. The use of rFVIIa outside its current licensed indications should be restricted to clinical trials.

3.4.2 BMJ Clinical Evidence

ไม่พบข้อมูลที่เกี่ยวข้อง

3.4.3 NHS evidence

1) ข้อมูลการศึกษาในผู้ป่วย haemophilia

พบว่าการศึกษาที่หาข้อสรุปด้านประสิทธิภาพ พบว่า rFVIIa มีประสิทธิภาพไม่น้อยไปกว่ากลุ่มควบคุม (activated prothrombin complex concentrate) และไม่มีรายงานด้านความปลอดภัยที่น่ากังวลเมื่อเทียบกับประโยชน์ที่ได้รับ[3] (#ref 4)

การศึกษาที่หาข้อสรุปด้านเศรษฐศาสตร์ พบว่าการใช้ rFVIIa ในผู้ป่วยฮีโมฟีเลียระดับอ่อน (mild) มีค่าใช้จ่ายสูงกว่า activated prothrombin complex concentrate[22] (#ref 7) แต่ผู้ป่วยฮีโมฟีเลียระดับอ่อน-ปานกลาง หรือ ปานกลาง-รุนแรง กลับมีค่าใช้จ่ายต่ำกว่า[19-21] (#ref 1, 3, 5,)

1. A cost evaluation of treatment alternatives in mild-to-moderate bleeding episodes in haemophilia patients with inhibitors in Turkey

Dundar S, Zulfikar B, Kavakli K, Gonen C, Zulfikar H, Yilmaz D, Hart W M, Sumen A, Tuna S, Karamalis M

Health technology

The use of recombinant activated Factor VII (rFVIIa), high-dose Factor VIII, prothrombin complex concentrate (PCC) and activated PCC (aPCC) for the treatment of acute bleeding episodes in haemophilia patients with inhibitors.

Effectiveness results

The percentage of bleedings achieving a successful outcome with each agent was 89.3% with rFVIIa, 71.4% with high-dose FVIII, 66.7% with aPCC and 80% with PCC.

The mean time to resolution of bleeding episodes was 17.3 hours with rFVIIa, 23.0 hours with high-dose FVIII, 43.6 hours with aPCC and 40.2 hours with PCC.

The mean number of days of hospitalisation per bleeding episode was 1.12 with rFVIIa, 1.16 with high-dose FVIII, 1.89 with aPCC and 0.72 with PCC.

The reader is referred to the 'Estimates of Effectiveness and Key Assumptions' section below for the effectiveness estimates included in the model.

No safety issues were reported with any treatment.

Clinical conclusions

The results of the observational study suggested that rFVIIa was more effective and provided a faster time to resolution of bleeding than the other agents.

Cost results

The overall total cost was TRL 13,348 (US$9,113) for rFVIIa, TRL 18,370 (US$12,542) for aPCC, TRL 22,080 (US$15,075) for high-dose factor VIII, and TRL 13,639 (US$9,128) for PCC.

The results of the sensitivity analysis showed that varying the parameters with uncertainty always yielded rFVIIa as the cheaper option.

Authors' conclusions

The results of the study showed that recombinant activated Factor VII (rFVIIa) and prothrombin complex concentrate (PCC) are associated with similar direct treatment costs that are lower than those associated with other first-line options. However, rFVIIa had higher efficacy than PCC and may, therefore, be considered the agent of choice for the treatment of haemophilia patients with inhibitors in Turkey.

2. Cost-utility analysis of recombinant factor VIIa (NovoSeven) in six children with long-standing inhibitors to factor VIII or IX

Ekert H, Brewin T, Boey W, Davey P, Tilden D

Health technology

The use of recombinant factor VIIa (rFVIIa) for the treatment of children with haemophilia and inhibitors to factor VIII or IX. The treatment consisted of an intravenous push injection of rFVIIa in a dose of 90 microg/kg, repeated in two hours. The treatment was mainly administered at home.

Clinical conclusions

The effectiveness evidence showed that the use of rFVIIa represented a safe intervention and improved quality of life, as perceived by the patients and parents.

Cost results

The total annual costs per patient were $189,313 with usual care and $219,214 with rFVIIa. This resulted in an extra cost of $29,901 with rFVIIa.

Synthesis of costs and benefits

An incremental cost-utility analysis was carried out to combine the costs and benefits of the interventions. The extra cost per additional QALY gained with rFVIIa over usual care was $51,553. The sensitivity analyses found that the variables that most affected the results were the usage and cost of replacement products.

Authors' conclusions

Treatment with recombinant factor VIIa (rFVIIa) proved to be cost-effective, with an incremental cost per quality-adjusted life-year (QALY) similar to that of other accepted health interventions.

3. Pharmacoeconomic analysis of recombinant factor VIIa versus APCC in the treatment of minor-to-moderate bleeds in hemophilia patients with inhibitors

Joshi A V, Stephens J M, Munro V, Mathew P, Botteman M F

Health technology

The study examined three regimens for home treatment of minor-to-moderate bleeds in haemophilia patients with inhibitors. The regimens consisted of first-, second- and third-line treatments using recombinant activated Factor VII (rFVIIa) and activated prothrombin-complex concentrate (APCC).

The first regimen (APCC-APCC-rFVIIa) was APCC (first-line), followed by another APCC (second-line) in case of failure of the first-line treatment, and then rFVIIa (third-line) in case of failure of the second-line treatment.

The second regimen (APCC-rFVIIa-rFVIIa) was APCC (first-line), followed by rFVIIa (second-line) in case of failure of the first-line treatment, and then by another course of rFVIIa (third-line) in case of failure of the second-line treatment.

The third regimen (rFVIIa-rFVIIa-rFVIIa) was rFVIIa as first-, second- and third-line treatments.

Cost results

Total home treatment costs after three lines of treatment were $32,331 with APCC-APCC-rFVIIa, $30,951 with APCC-rFVIIa-rFVIIa, and $28,101 with rFVIIa- rFVIIa- rFVIIa.

The rFVIIa only strategy was less expensive because of the lower re-bleeding rates, which led to lower requirements for second- and third-line treatments.

The results of the univariate sensitivity analysis corroborated the base-case findings since the rFVIIa-rFVIIa-rFVIIa regimen was the least expensive treatment in most scenarios.

The APCC-rFVIIa-rFVIIa regimen was never the cheapest treatment, and was preferred only when the mean dose of APCC decreased by 20% or when the mean dose of rFVIIa increased by 20%.

The threshold analysis showed that keeping the APCC efficacy at the base-case rate, the rFVIIa efficacy rate should decrease to 82% (92% in the base-case) for the overall cost of the treatment regimens to be the same between the rFVIIa-only strategy and APCC-continuing strategies.

The probabilistic analysis showed that the rFVIIa-rFVIIa-rFVIIa regimen was less expensive than the other two regimens in 68% of simulations. The APCC-rFVIIa-rFVIIa regimen was less expensive in 14% of simulations, and the APCC-APCC-rFVIIa regimen was less expensive in 18% of simulations.

Synthesis of costs and benefits

A synthesis of the costs and benefits was not relevant as the three regimens were equally effective when the third-line treatment was administered. Consequently, all patients were assumed to finally resolve the bleeding episode.

Authors' conclusions

The use of a recombinant activated Factor VII (rFVIIa) regimen for the home treatment of minor-to-moderate bleeds in haemophilia patients in the USA led to cost-savings in comparison with strategies involving activated prothrombin-complex concentrate (APCC), through the avoidance of second- and third-lines of treatment. The results were robust to variations in some clinical and economic data.

4. Control of bleeding in patients with haemophilia A with inhibitors: a systematic review

Lloyd Jones M, Wight J, Paisley S, Knight C

Results of the review

rFVIIa (15 studies).

Acute bleeding episodes: the studies were of a poor quality. rFVIIa was reported as being effective in: 71 to 93% of patients with joint, muscle or mucocutaneous bleeding (4 uncontrolled prospective trials); 62 to 100% of patients with severe bleeding (6 uncontrolled prospective trials, 1 study of pooled data and 1 case series); 78 to 88% of patients with central nervous system bleeding (3 uncontrolled prospective trials); and in 75 and 100% of patients during immune tolerance induction (1 uncontrolled prospective trial and 1 case series).

Surgery: rFVIIa was reported as being effective in 60 to 100% of patients with bleeding events during surgery (1 RCT, 3 uncontrolled prospective trials and 3 case series). The highest quality evidence for surgery was from one small RCT, which reported treatment success as being 67% with low-dose rFVIIa and 93% with high-dose rFVIIa.

Adverse events.

Several studies reported adverse events, including mild pyrogenic reactions/fevers, rashes/hives/urticaria, chills/shivering, dizziness, nausea, headache, lumbar pain, anaphylactic reactions, thrombocytopaenia, anamnesis, abdominal pain and a transient drop in blood-pressure. These were discussed in more detail in the review.

Authors' conclusions

There was no evidence to support the use of high-dose FVIII in bleeding episodes, although it was found to be successful for low-titre, low-responding inhibitors in surgery. pFVIII was effective in controlling severe bleeding with high-titre or high responding inhibitors, and in 60 to 90% of surgical procedures. aPCCs appeared more effective than PCCs in the control of mild to severe bleeding. rFVIIa controlled 70 to 100% of mild to severe bleeding episodes with high-responding inhibitors, and achieved better results when used early. There was no evidence for the use of PCCs in surgery. However, aPCCs controlled 90% of surgical episodes while rFVIIa controlled 60 to 100%.

5. Modelling the economic impact of recombinant activated Factor VII compared to activated prothrombin-complex concentrate in the home treatment of a mild to moderate bleed in adults with inhibitors to clotting Factors VIII and IX in the UK

Odeyemi I A, Guest J F

Cost results

The expected costs were 12,944 with rFVIIa and 14,645 with aPCC.

The estimated costs were sensitive to the number of doses and dosages of the study drugs, the probability of successful treatment at home, and the time to a bleed being resolved at home following initial treatment with either study drug.

However, the authors noted that the relative economic impact of rFVIIa was not sensitive to the number of doses and dosage of any drugs administered second-line or later, or any other component of treatment.

The probability that the expected cost per bleeding episode was below 10,000 was 77% with rFVIIa and 68% with aPCC.

Synthesis of costs and benefits

The costs and benefits were not combined because rFVIIa was both more effective and less costly than aPCC (rFVIIa dominant strategy).

Authors' conclusions

The use of recombinant activated Factor VII (rFVIIa) at home instead of activated prothrombin-complex concentrate (aPCC) approximately halved the time to resolving a minor bleeding episode while being, at the least, cost neutral.

CRD COMMENTARY - Selection of comparators

The rationale for the choice of the comparators was clear. The authors stated that aPCC and rFVIIa are commonly used in patients with high titre and high responding inhibitors (greater than 10 BU), who do not respond to conventional therapies. However, since the NHS had not advised on implementing UK guidelines, there was no consensus on the role of the different products. You should decide whether they are valid comparators in your own setting.

6. Optimising immune tolerance induction strategies in the management of haemophilia patients with inhibitors: a cost-minimisation analysis

Odeyemi IA, Dano AM

CRD summary

The primary objective was to explore the impact of non-immunogenic rather than immunogenic bypassing agents for the control of bleeds prior to immune tolerance induction (ITI) in haemophilia patients with inhibitors. The authors concluded that recombinant activated factor VII was the preferred agent in the management of these patients before ITI, from the perspective of the UK National Health Service. The study was well conducted and satisfactorily presented, which enhances the validity of the authors' conclusions.

Results

The mean cost of treatment, from detection of titres through ITI, per patient was £959,250 (SD 593,325) with APCC, and £770,834 (SD 588,951) with rFVIIa. The absence of anamnestic response in the rFVIIa arm explained 68% of the cost difference.

When considering the effectiveness of ITI, the mean cost per patient effectively able to tolerate treatment was £1,505,279 in the APCC arm and £1,196,706 in the rFVIIa arm.

The sensitivity analysis identified the unit cost and dosage of rFVIIa as the most influential model inputs, but they would have to triple in order to change the conclusions.

The probabilistic analysis indicated that the probability of the cost of an ITI being greater than £1 million was greater in patients whose bleeding episodes prior to ITI were managed with APCC compared with patients managed with rFVIIa.

Authors' conclusions

The authors concluded that rFVIIa was the preferred strategy in the management of patients with inhibitors, before ITI, from the perspective of the UK NHS.

7. A cost minimization model for the treatment of minor bleeding episodes in patients with haemophilia A and high-titre inhibitors

Putnam K G, Bohn R L, Ewenstein B M, Winkelmayer W C, Avorn J

Health technology

Two haemostatic agents for the home treatment of minor bleeding episodes in paediatric patients with haemophilia A and inhibitory antibodies to factor VIII (FVIII) were examined. The haemostatic agents studied were activated prothrombin complex concentrates (aPCC) and recombinant factor VIIa (rFVIIa).

Cost results

The estimated cost of a home treatment course was $21,000 with aPCC and $33,400 with rFVIIa. The sensitivity analysis showed that the base-case cost-difference was not sensitive to plausible variations in clinical data, prices and doses. The preferred strategy changed only when clinically unlikely changes in baseline values were considered. When panellists were asked to estimate the overall dosage for each treatment strategy, the total regimen costs were still lower with aPCC.

Synthesis of costs and benefits

A synthesis of the costs and benefits was not relevant since a cost-minimisation analysis was performed.

Authors' conclusions

The use of activated prothrombin complex concentrates (aPCC) as the first-line home haemostatic treatment for minor bleeding episodes in children with haemophilia A and inhibitory antibodies to factor VIII (FVIII) led to cost-savings in comparison with recombinant factor VIIa (rFVIIa).

2) ข้อมูลที่ไม่ใช่ผู้ป่วย haemophilia

ผู้ป่วยที่ไม่ใช่ฮีโมฟีเลียบางกลุ่มเท่านั้นที่อาจได้รับประโยชน์จากการใช้ rFVIIa (body trauma) นอกจากนั้น การใช้แบบ off-label ไม่ได้ช่วยลดอัตราการตายหรือทำให้ผลลัพธ์ในการรักษาดีขึ้น และทำให้ผู้ป่วยที่มีเลือดใน intracranial หรือผู้ป่วยผ่าตัดหัวใจต้องประสบกับ thromboembolic events ที่สูงขึ้น[10, 11]

1. Yank V, Tuohy CV, Logan AC, Bravata DM, Staudenmayer K, Eisenhut R, Sundaram V, McMahon D, Stave CD, Zehnder JL, Olkin I, McDonald KM, Owens DK, Stafford RS. Comparative Effectiveness of Recombinant Factor VIIa for Off-Label Indications vs. Usual Care. Comparative Effectiveness Review No. 21. (Prepared by Stanford-UCSF Evidence-based Practice Center under Contract No. #290-02-0017) Rockville, MD: Agency for Healthcare Research and Quality. May 2010. Available at: www.effectivehealthcare.ahrq.gov/reports/final.cfm.

Conclusions Available evidence on off-label rFVIIa use is limited across a wide spectrum of off-label indications. Considering the evidence as a whole, off-label rFVIIa may provide some benefit for certain clinical indications, but this conclusion is largely based on indirect outcomes that have an uncertain relationship to patient survival or functional status. Of the indications we studied, the benefit-to-risk ratio may be more favorable for body trauma than for other indications, because its use may reduce the occurrence of acute respiratory distress syndrome (ARDS); however, the strength of evidence is low for this as well as most other outcomes, which precludes definitive conclusions. Available evidence does not indicate that use of off-label rFVIIa reduces mortality or improves other direct outcomes for the indications we studied. Thromboembolic events are increased by use of rFVIIa in intracranial hemorrhage and adult cardiac surgery. Despite this state of evidence, in-hospital, off-label cases of rFVIIa use have increased in the last decade, particularly for cardiac surgery, trauma, and intracranial hemorrhage.

3.4.4 Systematic reviews ซึ่งสืบค้นจาก Pubmed

จากการสืบค้นฐานข้อมูล Pubmed ด้วยคำสำคัญ (("Factor VIIa"[Mesh] OR "recombinant FVIIa" [Supplementary Concept]) AND "Systematic"[Sb]) NOT "Randomized Controlled Trial" [Publication Type] เมื่อวันที่ 4 กรกฎาคม 2554 พบทั้งหมด 86 ผลลัพธ์ คัดเลือกเฉพาะผลลัพธ์ที่เกี่ยวข้องเหลือ 9 ผลลัพธ์

ผลการสืบค้น ได้ผลลัพธ์เช่นเดียวกับ NHS evidence กล่าวคือ ผลลัพธ์ในเชิงประสิทธิภาพของ rFVIIa ในผู้ป่วยฮีโมฟีเลียสรุปได้ว่ามีประสิทธิภาพ หรือไม่ด้อยไปกว่ากลุ่มควบคุม (เช่น factor VIII concentrate, activated prothrombin complex concetrate)[2-8] [#ref 1, 3, 5, 6, 7, 8, 11] และผลการศึกษาทางเศรษฐศาสตร์ rFVIIa ประหยัดค่าใช้จ่ายมากกว่ากลุ่มควบคุม[4] [#ref 4]

สำหรับข้อมูลในผู้ป่วย Glanzmann's thrombasthenia มีข้อมูลในลักษณะ case reports เท่านั้น[9] [#ref 2]

1. Recombinant Factor VIIa concentrate versus plasma derived concentrates for the treatment of acute bleeding episodes in people with haemophilia and inhibitors.

Iorio A, Matino D, D'Amico R, Makris M.

MAIN RESULTS:

A total of ten trials were identified, two of which (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 (rFVIIa and aPCC appeared to have a similar haemostatic effect in both studies, without increasing thromboembolic risk.

AUTHORS' CONCLUSIONS:

Although the main conclusion should be the need for further randomised controlled trials, we conclude that both rFVIIa and aPCC can be used to treat bleeding in haemophiliacs with inhibitors.

2. Thromb Haemost. 2009 Dec;102(6):1157-64.

Glanzmann's thrombasthenia (defective platelet integrin alphaIIb-beta3): proposals for management between evidence and open issues.

Di Minno G, Coppola A, Di Minno MN, Poon MC.

Introduction

Glanzmann's Thrombasthenia (GT) is a rare (~600 cases worldwide so far described) autosomal recessive bleeding disorder, characterised by a quantitative or qualitative defect of platelet surface □IIb-□3 integrin (GpIIbIIIa, fibrinogen receptor) leading to the failure of platelets to bind fibrinogen, retract a fibrin clot or aggregate after stimulation by agonists such as ADP, thrombin, epinephrine, or collagen alone or in combination (1–3). At variance with its usual incidence (about 1 in a million), higher figures are reported in certain populations where consanguineous marriages are frequent, in particular in the Middle East (4–7). Most patients (>2/3) require blood and/or platelet transfusions at least once in their life (7, 8). GT is therefore considered a severe haemorrhagic disease. However, bleeding phenotype is dramatically variable, some patients having only minimal bruising, others frequent, severe, potentially fatal haemorrhages.

Presently, no specific guidelines or algorithms for clinical management of GT are available. On the basis of a review of the literature, we briefly discuss clinical features and the available strategies for treatment of GT patients, with the aim of proposals for the management of the different clinical conditions in this setting.

Management (print หน้า 8 ของ pdf หรือ 1159 ของบทความ)

Recombinant activated factor VII (rFVIIa)

Because of its ability at high doses to improve the impaired thrombin generation of GT patients through the direct activation of FX on platelet surface and to partially restore platelet aggregation, possibly through the involvement of other membrane receptor pathways (42–43), recombinat activated factor VII (rFVIIa) provides an alternative haemostatic strategy in this setting.

After the first successful use in 1996 in a GT child with severe recurrent epistaxis (44), many case reports and some case series of rFVIIa for prophylaxis and treatment of bleeding in GT patients have been published over the last decade (44–47). In 2004 the results of an international survey evaluating the use of rFVIIa in 59 GT patients (1–72 yrs, median 22, of

whom 42% had anti-HLA or anti-□IIb-□3 alloantibodies) for 108 bleeding episodes (76 severe, 32 moderate; 45 nose, 29 oropharyngeal, 17 gastrointestinal), and 34 invasive procedures (9 major, 12 minor surgery, 13 dental procedures) were published (16). With the obvious limitations of its retrospective design, this survey represents the largest collection of treatments in GT patients and provided broad suggestions for clinical use of rFVIIa in this setting:

1) success rates with rFVIIa bolus injections are highest with 'optimal' regimens, defined as treatments with dosage ≥80 µg/kg at intervals of ≤2.5 hours, for at least 3 doses;

2) success rates are lower in gastrointestinal bleedings, where local causes of bleeding often co-exist;

3) continuous infusion is successful for surgical procedures;

4) as previously reported in the series published by Almeida et al (46), regardless of dosing and/or scheduling, rFVIIa treatment, if used, should be started early (83% success within 6 hours) after bleeding onset;

5) the use of rFVIIa is safe, being associated with severe adverse events in 2 cases (1.4%), both occurring in subjects with risk factors for clotting, in addition to receiving rFVIIa by prolonged continuous infusion at high dose (25–30 µg/kg/ hour) and on simultaneous treatment with antifibrinolytic agents. Cancer, age and prolonged bed rest were the risk factors in a subject that developed bilateral deep vein thrombosis and pulmonary embolism; gynaecological surgery had been recently carried out in a patient that developed a clot in the renal pelvis and ureter.

Presently, rFVIIa is licensed in the EU for GT patients with platelet alloimmunisation and history (past or present) of platelet refractoriness (Table 4).

In patients with circulating isoantibodies and severe/lifethreatening bleeding, the combined use of rFVIIa with high-dose HLA-matched platelets and/or removal of isoantibodies by apheresis/immunoabsorption have been reported (40, 48, 49).

3. Haemophilia. 2009 Mar;15(2):420-36.

Efficacy of recombinant activated factor VII vs. activated prothrombin complex concentrate for patients suffering from haemophilia complicated with inhibitors: a Bayesian meta-regression.

Treur MJ, McCracken F, Heeg B, Joshi AV, Botteman MF, De Charro F, Van Hout B.

Abstract

The optimal on-demand treatment of joint bleeds in haemophilia patients with inhibitors is a source of debate, with studies reporting various efficacy levels for different drugs and dosage regimens. To analyse, in a unified Bayesian meta-regression model, the published efficacy of recombinant activated factor VII (rFVIIa) and/or activated prothrombin complex concentrate (aPCC) as on-demand treatments for joint bleeds in haemophilia patients with inhibitors. A **systematic** search was carried out to identify studies reporting on dosage and efficacy of rFVIIa and aPCC in the treatment of joint bleeds in the target patient population. Data were abstracted and included in the model and adjusted for potential sources of heterogeneity. Pooled efficacy levels for typical rFVIIa and aPCC regimens were estimated. Seventeen studies, collectively reporting on >2000 joint bleeds, were included. Medication type combined with dosage was the only significant explanatory parameter. The model predicts that a typical regimen of 90 microg kg(-1) rFVII repeated every 3 h if needed results in cumulative joint bleed resolution of 66%, 88% and 95% after 12, 24 and 36 h, respectively. In comparison, a typical regimen of 75 IU kg(-1) aPCC repeated every 12 h if needed results in cumulative joint bleed resolution of 39%, 62% and 76%, respectively. These differences were statistically significant and were also robust in sensitivity analyses. This analysis suggests that a typical rFVIIa regimen will resolve joint bleeds more effectively than a typical aPCC regimen after 12, 24 and 36 h.

4. Haemophilia. 2009 Mar;15(2):405-19. Epub 2009 Feb 1.

A systematic review of the cost-effectiveness of rFVIIa and APCC in the treatment of minor/moderate bleeding episodes for haemophilia patients with inhibitors.

Knight C, Danø AM, Kennedy-Martin T.

Abstract

The clinical, humanistic and economic consequences associated with haemophilia and inhibitors are considerable. Primary treatment for mild-to-moderate bleeding disorders in such patients is recombinant factor VIIa (rFVIIa) or activated prothrombin complex concentrate (APCC). The aims of this study were to identify, review and evaluate the quality of the published literature on the relative cost-effectiveness of rFVIIa and APCC in treating haemophilia patients with inhibitors. The review concentrates on model type, design and assumptions, and results. The results of this study suggest that rFVIIa may be the cost-effective alternative to treatment with APCC. In seven out of the nine studies, rFVIIa had the lower average treatment cost. The difference in average treatment cost to resolve a bleed, between rFVIIa and APCC in these seven studies, ranged from $3000 to $17 000. The adapted modelling framework is similar in all the economic models reviewed, suggesting clinical acceptability of the approach used. The estimates of efficacy varied between the models, especially for APCC. The efficacy for APCC derived from retrospective studies was lower than reported in the literature. Sensitivity analysis was undertaken in the majority of the economic analyses and the results were found to be robust to realistic parameter variations. Only one of the studies was a cost-utility study, showing the lack of measuring health status within this area. This systematic review showed that models based on different sources of data produced fairly similar robust results despite differences in the estimates of efficacy, average dosage required, and unit costs. However, ideally there should be a systematic approach to identifying the relevant data.

5. Adv Ther. 2009 Jan;26(1):68-88. Epub 2009 Jan 20.

Systematic review of efficacy of rFVIIa and aPCC treatment for hemophilia patients with inhibitors.

Knight C, Danø AM, Kennedy-Martin T.

bstract

INTRODUCTION:

The primary treatment for mild-to-moderate bleeding disorders in hemophilia is either recombinant activated factor VII (rFVIIa) or activated prothrombin complex concentrate (aPCC). The efficacy of both products has been evaluated in individual studies; however, there has not been an overall review to compare the efficacy from these individual studies of rFVIIa and aPCC. Our aim is to establish robust estimates of the efficacy, speed of bleed resolution, and adverse event profile of both rFVIIa and aPCC.

METHODS:

A systematic review was conducted of the relevant literature.

RESULTS:

We identified 11 open-label cohort studies, six randomized clinical trials, including two head-to-head clinical trials, and a meta-analysis. The definition of efficacy varies between these studies, but is usually a composite measure of definite pain relief, reduction in the size of the hemorrhage, and cessation of bleeding. The individual making the interpretation of efficacy and the time from treatment initiation to recording the efficacy endpoint also varies across the studies. Overall, estimates of efficacy from randomized clinical trials using dosing regimens in line with the guidelines are higher for rFVIIa (81%-91%) than for aPCC (64%-80%). Conclusions from a meta-analysis suggest that treatment with rFVIIa may be associated with a faster time to joint bleed resolution than aPCC due to higher efficacy levels at different time points. The results from a comparative trial support the improved efficacy rates associated with rFVIIa compared with aPCC.

CONCLUSION:

The wide variations in definitions of efficacy and study methods make comparison of results across studies difficult. Further head-to-head trials should incorporate a standardized measurement for defining efficacy.

6. Transfus Apher Sci. 2008 Feb;38(1):25-32. Epub 2008 Feb 11.

Evidence-based use of recombinant FVIIa (NovoSeven, NiaStase) for the treatment of hemophilia with inhibitors in children and adolescents.

Goldstein B, Geldziler B, Bjerre J, Seremetis S.

Abstract Children and adolescents comprise a significant proportion of the hemophilia population, including those patients who have developed inhibitors to factor VIII or FIX. We examine the use of rFVIIa for the treatment of bleeding episodes and the prevention of bleeding in children and adolescents with hemophilia A and B with inhibitors, focusing on registry data and recent clinical trial results. Based on this review of the literature, we conclude that recombinant FVIIa is safe and effective for use in controlling bleeding in these patient populations.

7. Haemophilia. 2007 Sep;13(5):451-61.

Treatment of acquired haemophilia with recombinant activated FVII: a critical appraisal.

Sumner MJ, Geldziler BD, Pedersen M, Seremetis S.

Source Novo Nordisk Inc., 100 College Road West, Princeton, NJ 08540, USA. mcsm@novonordisk.com

Abstract Acquired haemophilia is a rare bleeding disorder usually caused by the spontaneous formation of inhibitory antibodies to coagulation FVIII. The disease occurs most commonly in the elderly, and although acquired haemophilia may be associated with a variety of underlying conditions, up to 50% of reported cases are idiopathic. Treatment options have traditionally involved human FVIII or FIX replacement therapy (if the inhibitor titre allows), porcine FVIII or the use of activated pro-thrombin complex concentrates. Recombinant activated coagulation FVII (rFVIIa) was available on an emergency and compassionate use basis from 1988 to 1999 at sites in Europe and North America. It has been registered in Europe for use in treating acquired haemophilia since 1996 and has recently been licensed for this indication in the United States. By directly activating FX on the surface of activated platelets at the site of injury (thereby bypassing FVIII and FIX), rFVIIa can circumvent the actions of inhibitory antibodies present in acquired haemophilia patients. This paper provides an overview of experiences with rFVIIa for the treatment of acquired haemophilia from the NovoSeven compassionate and emergency use programmes (1989-1999), the Hemophilia and Thrombosis Research Society Registry, and independent published reports from January 1999 to September 2005. rFVIIa has been reported to provide safe and effective haemostasis as a first line therapy in patients of all ages for a variety of surgical and non-surgical bleeding situations.

8. Haemophilia. 2006 Jan;12(1):19-27.

Congenital factor VII deficiency: therapy with recombinant activated factor VII -- a critical appraisal.

Mariani G, Konkle BA, Ingerslev J.

Source Department of Internal Medicine and Public Health, University of L'Aquila, L'Aquila, Italy. gmariani@cc.univaq.it

Abstract Congenital factor VII (FVII) deficiency is a rare bleeding disorder with high phenotypic variability, and optimal management has yet to be determined. Treatment has traditionally involved FVII replacement therapy using fresh frozen plasma, prothrombin complex concentrates or plasma-derived FVII concentrates. Recombinant activated FVII (rFVIIa, NovoSeven(R)), the first recombinant treatment option, has recently been approved in the European Union for use in congenital FVII deficiency, but has been available on an emergency and compassionate use basis since 1988. In FVII deficiency, rFVIIa serves as substitution therapy as it provides the physiological ligand (FVIIa) for tissue factor, its receptor exposed at the site of vascular injury. This paper provides an overview of published and unpublished experience with rFVIIa in patients with congenital FVII deficiency from the NovoSeven compassionate and emergency use programmes (1988-99) and of independent reports in the literature. Recombinant FVIIa has been reported to provide effective haemostasis in patients of all ages and in a range of bleeding situations, including acute central nervous system/life-threatening bleeding episodes (15 episodes in 12 patients), non-life-threatening bleeding episodes (>32 episodes in 17 patients), surgery (>40 interventions in 25 patients) and childbirth (three women). Preliminary reports suggest that it may

also be effective prophylactically. The risk of thrombosis in FVII-deficient patients treated with rFVIIa is unknown, as is the occurrence of inhibiting antibodies. A postlicensure pharmacovigilance registry (Seven Treatment Evaluation Registry) has been set up to continue to monitor the efficacy and safety (including alloantibody development) of rFVIIa in patients with FVII deficiency.

9. Crit Care Med. 2005 Apr;33(4):883-90.

Efficacy and safety of recombinant factor VIIa for treatment of severe bleeding: a systematic review.

Levi M, Peters M, Büller HR.

Source

Department of Vascular Medicine/Internal Medicine, Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands.

Abstract

BACKGROUND:

Recombinant activated factor VII (**factor VIIa**) is a prohemostatic agent that can be used for patients with complicated coagulation disorders. Recombinant **factor VIIa** is, however, increasingly used for several other indications, including patients with a preexistent normal coagulation system but who experience serious bleeding, for example, after major surgery or trauma.

DATA SOURCE:

We performed a **systematic** review of all published and unpublished clinical studies using MEDLINE (1966-2004) and all other sources available to assess the available evidence on the efficacy and safety of recombinant **factor VIIa** in patients with or without coagulation disorders.

STUDY SELECTION:

We found 483 articles related to the pharmacologic use of recombinant **factor VIIa**, including 28 clinical trials, 124 case series, and 176 case reports, which were all considered for this review.

DATA SYNTHESIS:

Recombinant **factor VIIa** is an effective and relatively potent prohemostatic agent in approximately 90% of patients with hemophilia and inhibiting antibodies and other types of complex coagulation disorders. The application of recombinant **factor VIIa** in other patients who experience severe bleeding is promising, and although sound evidence from controlled clinical trials is only scarcely available so far, forthcoming trials are likely to provide more substantiation for this use. Recombinant **factor VIIa** appears to be relatively safe with a 1-2% incidence of thrombotic complications based on published trials.

CONCLUSIONS:

More randomized controlled clinical trials are required to assess the efficacy and safety of recombinant **factor VIIa** for patients without a preexistent coagulation disorder and with severe bleeding. In the meantime, off-label use of recombinant **factor VIIa** may be considered in patients with life-threatening bleeding.

10. Cochrane Database Syst Rev. 2004;(2):CD004449.

Recombinant Factor VIIa concentrate versus plasma derived concentrates for the treatment of acute bleeding episodes in people with Haemophilia A and inhibitors.

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Source

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Update in

- Cochrane Database Syst Rev. 2010;(8):CD004449.

Abstract

BACKGROUND:

In some people with haemophilia, therapeutic clotting agents are recognised as a foreign protein and anti-FVIII antibodies, known as 'inhibitors', are produced. This review investigates which treatment most effectively arrests acute bleeding in people with haemophilia A and inhibitors.

OBJECTIVES:

To determine the clinical effectiveness of **recombinant FVIIa** concentrate in comparison to plasma-derived concentrates for the treatment of acute bleeding episodes in people with haemophilia A and inhibitors.

SEARCH STRATEGY:

We searched the Cochrane Cystic Fibrosis and Genetic Disorders Group trials register which comprises of references identified from comprehensive electronic database searches and handsearching of relevant journals and abstract books of conference proceedings. Date of the most recent search of the Group's trials register: September 2003.

SELECTION CRITERIA:

Randomised (RCTs) and quasi-randomised controlled clinical trials comparing **Recombinant FVIIa** concentrate to human plasma-derived concentrates (high-dose human or recombinant FVIII concentrate; prothrombin complex concentrates (PCCs); activated prothrombin complex concentrate (aPCC)) in people with haemophilia A. Comparisons with animal derived products were excluded.

DATA COLLECTION AND ANALYSIS:

No studies were found that were eligible for inclusion in this review.

MAIN RESULTS:

A total of four studies were identified by the searches, however, none of these were eligible for inclusion in this review.

REVIEWERS' CONCLUSIONS:

No RCTs on the relative effectiveness of **Recombinant FVIIa** concentrate compared to human plasma-derived concentrates in people with haemophilia A and inhibitors were identified for inclusion in this review. The research evidence on which to base clinical decisions is therefore limited to case reports, and other less robust evidence. There is need for a well-designed, adequately-powered randomised controlled trial to assess the relative benefits and risks of using **Recombinant FVIIa** concentrate compared to human plasma-derived concentrates in people with haemophilia A and inhibitors.

11. Haemophilia. 2003 Jul;9(4):464-520.

Control of bleeding in patients with haemophilia A with inhibitors: a systematic review.

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Abstract This paper reports a systematic review of the best available evidence of clinical effectiveness in the treatment of acute bleeding in haemophilia A patients with inhibitors. Because of the lack of randomized controlled trials (RCTs) on this topic, broad inclusion criteria with regard to study design were applied in order to assess the best available evidence for each intervention. Because of the clinical and methodological heterogeneity of the evidence, it was not appropriate to pool data across studies; instead, data were synthesized using tabulation and qualitative narrative assessment. No evidence was found to support the use of high-dose factor VIII (FVIII) in bleeding episodes. However in surgery it was found to be highly successful (100%) for low-titre, low-responding inhibitors although not reliable for high-responding inhibitors. Porcine FVIII (pFVIII) was effective in the control of severe bleeding episodes with high-titre or high-responding inhibitors

(100%) and in 60-90% of surgical procedures. Activated prothrombin complex concentrates (APCCs) appear to be more effective than prothrombin complex concentrates (PCCs) in the control of mild to severe bleeding episodes. There was no good evidence for the use of PCCs in surgery. APCCs controlled bleeding in approximately 90% of surgical episodes. Recombinant factor VIIa (rFVIIa) controlled 70-100% of mild to severe bleeding episodes with high-responding inhibitors, and achieved better results when used early. It was effective in 60-100% of surgical episodes. Doses varied from study to study, and side-effects from mild to infrequent but serious adverse events were reported. The quality of the evidence is variable. Limited evidence relating to other treatment options is also included in the review.

12. Semin Thromb Hemost. 2000;26(4):425-32.

Efficacy and safety of recombinant factor VIIa in the prophylaxis of bleeding in various surgical procedures in hemophilic patients with factor VIII and factor IX inhibitors.

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Abstract Patients with hemophilia may develop alloantibodies (inhibitors) directed toward the substitution factor. In the long term, this complication significantly affects around 15% of hemophilia A patients and 2-5% of hemophilia B patients suffering the severe class of disease (critical functional factor level <0.01 IU/mL). The typical consequence of a newly developed inhibitor is that the patient can no longer take advantage of the principles of modern hemophilia management, including safe and early treatment of bleeding and prophylactic use of concentrate in prevention of bleeding. Moreover, problems that are normally solved by means of a surgical procedure covered by the usual concentrate will be regarded as difficult and are likely to be associated with risk of untoward bleeding if high-titer inhibitors are present. Over the past decade, considerable experience has been collected illustrating that surgery may be performed quite safely in the patient with inhibitors if hemostasis is assisted by a new hemostatic agent, an activated recombinant factor VII molecule (rFVIIa). Although only one controlled randomized surgical study has been presented, cumulated data from this and from other, less formal studies on the use of rFVIIa in hemophilic inhibitor surgery have illustrated that a vast variety of different surgical procedures can be accomplished with none of the life-threatening bleeding complications that would be anticipated if no hemostatic treatment was administered. The aim of the present review is to present a multiplicity of surgical procedures that have been carried out during the clinical development of rFVIIa. Further, an update of 21 surgical procedures in inhibitor patients from the center of the author will be reviewed and discussed.

3.4.5 Randomized controlled trials ซึ่งสืบค้นจาก Pubmed

ไม่ได้ทำการสืบค้นเนื่องจากมีข้อมูลจาก systematic review เพียงพอแล้ว

3.5 ข้อมูลด้านค่าใช้จ่าย และการประเมินความคุ้มทางเศรษฐศาสตร์

ข้อมูลด้านความคุ้มค่าทางเศรษฐศาสตร์ได้สรุปไว้ใน NHS evidence (หัวข้อที่ 3.4.3 NHS evidence) และ Pubmed ส่วนที่เป็น systematic review (หัวข้อ 3.4.4 Systematic reviews ซึ่งสืบค้นจาก Pubmed) แล้ว

สำหรับคาดการณ์ค่าใช้จ่ายต่อผู้ป่วย 1 ราย ต่อการรักษาเลือดออก 1 ครั้ง ประมาณ 46,812 - 160,500 บาท (คำนวณโดยให้ยาครั้งละ 35 to 120 µg/kg และน้ำหนักผู้ป่วยเฉลี่ย 60 kg)[1]

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