National Essential Medicines List
Tertiary/Quaternary Medication Review Process
Bypassing Agents

Date: September 2017

Medication: Haemophilia bypassing agents

- Recombinant Factor VIIa (rVIIa)
- Activated Prothrombin Complex Concentrate (aPCC)

Indication: Haemophilia with inhibitors (on demand, when presenting with a significant bleed)

Introduction

Haemophilia refers to inherited bleeding disorders caused by deficiency of specific coagulation factors. Haemophilia A is caused by coagulation factor VIII (FVIII) deficiency, haemophilia B by deficiency of coagulation factor IX (FIX), and haemophilia C by deficiency of coagulation factor XI. These clotting factor deficiencies are caused by recessive mutations of the respective clotting factor genes.

Both diseases have the same clinical presentation, so their specific diagnosis must be established by factor assay. Haemophilia A has a prevalence of about 1 in 10 000 males, while haemophilia B is less common, with a prevalence of about 1 in 35 000 males.

Haemophilia A and B is treated using FVIII-replacement or Factor FIX therapy, but administration of the factor can lead to the development of anti-FVIII or FIX antibodies, commonly known as inhibitors. These inhibitors interfere with the factor function and prevent coagulation. Inhibitors are usually IgG antibodies that neutralise the procoagulant activity of FVIII or FIX. About 10 - 15% of haemophilia A patients and 1 - 3% of haemophilia B patients may develop persistent inhibitors, which make treatment with factor concentrates difficult.[1]

Haemophilia patients with inhibitors are at a higher risk of experiencing a bleeding episode and are more difficult to treat. Treatment of acute bleeding episodes in patients with high-responding inhibitors most often involves the use of bypassing haemostatic agents, such as plasma-derived activated prothrombin complex concentrates (aPCC) or recombinant activated Factor VII (rFVIIa).

Risk factors for the development of inhibitors include severe haemophilia and a family history of inhibitor development. Inhibitors are more common in black patients. If a child with haemophilia A is going to develop an inhibitor, this usually happens within the first 50 exposure days after starting FVIII replacement therapy.

Inhibitor titres are measured in Bethesda units (BU), with low-titre inhibitors measuring ≤5 BU and high-titre inhibitors measuring >5 BU. Inhibitor patients are further classified as high or low responders based on the way inhibitor titres change in response to treatment.

Contextualization

For haemophiliacs with high titre inhibitors, apart from the two bypassing haemostatic agents, there is no other treatment option available to stop bleeding. Life threatening bleeds such as intracranial or gastrointestinal bleeding will be associated with significant mortality, or prolonged ICU stay if bleeding cannot be controlled. Non-life threatening bleeds such as joint bleeds will over time lead to debilitating haemophilic arthropathy, rendering these patients disabled, and not

economically active. Furthermore, it is not possible to perform any surgical intervention (e.g. appendectomy) without bypassing haemostatic agent cover.

Current South African Haemophilia Society Treatment guidelines[1]:

Treatment of haemophilia A with inhibitors

Treatment regimen for bleeding episode

Low-responder inhibitors (<5 BU):

- Give pdFVIII (plasma-derived factor VIII) at a dose of 2 - 3 times the normal dose.
- Must monitor clinical response. If there is no response and inhibitor levels have increased, treat with one of the bypassing agents.

High-responder inhibitors:

- aPCC
    - Give dose of 50 - 100 IU/kg IV 12-hourly for 3 days.
    - Do not exceed a maximum dose of 200 IU/kg.
    - Guidelines advise against the use of antifibrinolytics (e.g. tranexamic acid) with aPCC, due to a theoretical risk of thrombosis. Some experts, however, feel that antifibrinolytics can be used safely as an adjunct to aPCC.

OR

- rFVIIa
    - Give dose of 90 - 120 µg/kg IV every 2 - 3 hours as bolus or 20 IU/kg/hour as continuous infusion.
    - Antifibrinolytic (tranexamic acid) can be given concurrently with rFVIIa.

Treatment of haemophilia B with inhibitors

- Both rFVIIa and aPCC are effective for treatment of acute bleeding episodes in patients with high titre and/or high responder inhibitors to FIX.
- aPCC use should be carefully monitored for anaphylaxis and anamnestic reaction.
- Patients with haemophilia B and inhibitors are best treated with rFVIIa, the only bypassing agent that does not contain FIX.
- There is no evidence to guide tolerisation procedures in patients with haemophilia B and inhibitors. Plasma-derived FIX may be used for tolerisation with careful monitoring of anaphylactic reactions.

Evidence synthesis and quality:

Efficacy

Recombinant Factor VIIa vs aPCC

One of the most widely quoted study comparing the two most commonly used bypassing agents, is the FENOC Study.[2] The FENOC study was designed to test equivalence of the products in the treatment of ankle, knee, and elbow joint bleeding. A prospective, open-label, randomized, crossover, equivalency design was used. The primary outcome was evaluation 6 hours after treatment. Data for 96 bleeding episodes contributed by 48 participants was analysed. The criterion for declaring the 2 products equivalent at 6 hours was not met; however, the confidence interval of the difference in percentage efficacy reported for each product only slightly exceeded the 15% boundary (11.4%-15.7%), P=0.059. aPCC and rFVIIa appear to exhibit a similar effect on joint bleeds.

In a more recent study performed by Treur et al.[3] 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 90mcg/kg rFVII repeated every 3 hours if needed results in cumulative joint bleed resolution of 66%, 88% and 95% after 12, 24 and 36 hours, respectively. In comparison, a typical regimen of 75 IU kg aPCC repeated every 12 hours if needed results in cumulative joint bleed resolution of 39%, 62% and 76%, respectively. This analysis suggests that a typical rFVIIa regimen will resolve joint bleeds more effectively than a typical aPCC regimen after 12, 24 and 36 hours.
A 2015 Cochrane review[4] included two RCT's (Astermark 2007, and Young 2008). Both trials had significant quality issues, but the conclusion of the Cochrane review was that based on available randomized evidence aPCC and rVIIa are equally effective in controlling bleeding. Both agents were deemed to be safe. A full meta-analysis could not be done due to differences in outcome measures between the two trials. The only statistically significant difference between aPCC and rVIIa was in the Young trial where more patients (8 vs. 2) required rescue treatment within 9 hours in aPCC group compared to 270ug/kg rVIIa group ($p = 0.032$).[4]

It is well described that there is marked variation in response to bypassing agents between specific individuals. There are even patients described who require sequential dosing with both agents to attain bleeding control. The reasons for this is not well understood, but may involve, amongst other reasons, antibodies against components of the agents (e.g. antibodies against rVIIa). Furthermore, there is variation between individuals in not only dose required, but also in effective dosing interval. Some patients may need rVIIa dosing every 2 to 3 hours (as in the standard dose interval), while others can safely be managed with doses every 6 hrs. Unfortunately, there is no way to clinically predict these factors, and it is usually a matter of trial and error. Traditional laboratory coagulation tests cannot predict response[5].

From the two available head-to-head comparison studies, only the FENOC study[2] is able to provide some insight into the frequency of such variability to response between the agents. In the FENOC 66 patients in 27 centres in Europe/North America were randomized in an open label fashion to aPCC or rVIIa for their 1st bleed, with crossover for the following bleeding episode to the other agent. These episodes were analysed as pairs. There was a high percentage of discordant pairs (in other words, one treatment effective/the other not effective), that ranged from 43.8% at 2 hours to 9.8% at 36 hours.

Consensus between experts is that approximately 30% of patients will show a preferential response to one or the other agent.

Safety
Both rFVIIa and aPCC have been shown to have similar safety.[4]

Cost
Cost efficacy data[6] is conflicting with 4/8 studies deeming aPCC more cost effective, and 4/8 studies deeming rVIIa more cost effective. Important point is that study sponsor's agent generally came out as the winner. Costs will be influenced by number of doses given and the setting where it is used. (e.g joint bleed vs prophylaxis for major surgery).

Cost comparison rFVIIa (Novoseven® available) and aPCC (FEIBA® available):

Minor Bleeds

FEIBA	Dose	Dose for 70kg patient	No. of 1000 U needed	No. of 500 U needed	Cost per 1000 U	Cost per 500U	Cost per dose	No. doses	Cost per treatment
	50 IU/kg	3500IU	3	1	R14,457.17	R7,228.95	R50,600.46	2	**R101,200.92**

Novoseven	Dose	Dose for 70kg patient	No. of 5mg needed	No. of 2mg needed	Cost per 5mg	Cost per 2mg	Cost per dose	No. doses	Cost per treatment
	0.09 ug/kg	6.3 ug	1	1	R30,868.50	R12,347.40	R43,215.90	2	**R86,431.80**

Major bleeds

FEIBA	Dose	Dose for 70kg patient	No. of 1000 U needed	No. of 500 U needed	Cost per 1000 U	Cost per 500U	Cost per dose	No. doses	Cost per treatment
	50 IU/kg	3500 IU	3	1	R14,457.17	R7,228.95	R50,600.46	4	**R202,401.84**

Novoseven	Dose	Dose for 70kg patient	No. of 5mg needed	No. of 2mg needed	Cost per 5mg	Cost per 2mg	Cost per dose	No. doses	Cost per treatment
	0.09 ug/kg	6.3 ug	1	1	R30,868.50	R12,347.40	R43,215.90	4	**R172,863.60**
	OR								
	0.27 ug/kg	18.9 ug	3	2	R30,868.50	R12,347.40	R117,300.30	1	**R117,300.30**

Summary:

The need for having a bypassing agent on the EML is recognized, as there is no alternative for patients with high titre inhibitors (>5 BU). Patients can present with acute life threatening bleeds, and unavailability of an effective agent will lead to significant increase in mortality. Chronic joint bleeds lead to permanent disability. There is no alternative treatment available for these patients. Surgical intervention also require cover with these agents.

Due to approximately 30% of patients responding preferentially to one of the agents, both agents is required.

Low titre (<5 BU), low responding (Not increasing >5 on Factor 8 challenge) could potentially be managed by high doses (2 to 3 times normal dose) of Factor VIII concentrate.

Recommendation:

The Committee recommends that one bypassing agent be available on the EML, as a class. The alternative bypassing agent should also be available as emergency stock on a named patient basis for patients not responding to the EML item. The use of these agents should be under the guidance of clinicians skilled in the management of patients with haemophilia. Their use should be managed and monitored by local Pharmacy and Therapeutics Committees. Where possible all haemophilia patients should be treated in haemophilia comprehensive care centers.

Review indicators:

- availability of novel bypassing agents
- health economic considerations

References:

[1] Mahlangu J, Gillham A. Treatment Guidelines for Haemophilia in South Africa. South African Medical Journal. February 2008, 98(2):127-138.

[2] Astermark J, Donfield SM, Gringeri A, Gilbert SA, Waters J, Berntop E. A randomized comparison of bypassing agents in hemophilia complicated by an inhibitor: the FEIBA NovoSeven Comparative (FENOC) Study. Blood 2007; 109: 546–51.

[3] Treur MJ, McCracken F, Heeg B et al. Efficacy of recombinant activated factor VII vs. activated prothrombin complex concentrate for patients suffering from haemophilia complicated with inhibitors: a Bayesian metaregression. Haemophilia 2009; 15: 420–36.

[4] Matino D, Makris M et al. Recombinant factor VIIa concentrate versus plasma-derived concentrates for treating acute bleeding episodes in people with haemophilia and inhibitors. Cochrane Database Syst Rev. 2015

[5] Young G, Blain R et al. Individualization of of bypassing agent treatment for haemophilic patients with inhibitors utilizing thromboelastography. Haemophilia 2006; 12: 598-604

[6] Baghaipour MR, Steen Carlsson K. Strategies for inhibitor treatment and costs in the short and long term: a critical evaluation of recent clinical studies. Eur J Haematol 2015 Feb 30-7