



GUIDELINES FOR THE TREATMENT OF INHIBITORS IN HAEMOPHILIA A AND HAEMOPHILIA B

**Australian Haemophilia Centre Directors'
Organisation**

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Disclaimer

This document is a general guide to appropriate practice, to be followed subject to the clinician's judgment and the patient's preference in each individual case. The guidelines are designed to provide information to assist decision-making and were reviewed in 2008.

These guidelines will be reviewed in 2011.

1. INTRODUCTION

The management of patients with haemophilia A and haemophilia B and inhibitors is complex and must be managed by a Haemophilia Treatment Centre (HTC). Major issues with treatment are firstly, the control of acute haemorrhage and secondly the eradication of the inhibitor (immune tolerance induction - ITI). A systematic review of management of inhibitors in haemophilia A and haemophilia B have been recently published [1, 2].

2. TOLERISATION ADVISORY COMMITTEE

Management of inhibitor patients is difficult. The Tolerisation Advisory Committee (TAC) is a subcommittee of AHCDO providing consultation on all cases of inhibitor patients and tolerisation (see TAC terms of reference on ACHDO website). In general, all cases of proposed ITI in Australia should be discussed in the setting of the TAC.

3. GENERAL COMMENTS

Approximately 25% of patients with severe Haemophilia A develop inhibitors after initial treatment with factor VIII concentrates [3]. Approximately half of these appear transient and disappear with continued therapy with factor VIII. Therefore the diagnosis of an inhibitor, irrespective of titre, requires active monitoring and treatment to determine whether the inhibitor progresses to a high titre inhibitor (>5BU) or is transient.

After initial diagnosis of a low titre inhibitor in a patient with Haemophilia A, routine doses of factor VIII may be as much as doubled and the clinical response and inhibitor titre monitored. Subsequent poor clinical response or rising titre levels indicate a non-transient inhibitor. The diagnosis of a high titre inhibitor which does not respond to factor VIII should be treated with an alternative product.

There is an incidence of inhibitors in those with mild Haemophilia A following treatment with factor VIII concentrates and the guidelines will also apply to those patients. DDAVP is occasionally used in mild to moderate haemophilia but is often ineffective [3].

The incidence of inhibitors in those with severe Haemophilia B is much less common (3%) but requires more careful individual management in a HTC. The immune based problems of anaphylaxis and nephrotic syndrome can occur in the setting of ITI as additional complication.[1]

4. CONTROL OF HAEMORRHAGE

4.1. Products Available

In Australia the main products available are

- factor VIII, either recombinant or plasma-derived
- recombinant factor VIIa
- activated prothrombin complex concentrate (eg FEIBA)
- prothrombin complex concentrate (eg prothrombinex-HT)
- antifibrinolytics (eg tranexamic acid)

Note: Porcine factor VIII is no longer being manufactured. A recombinant porcine factor VIII may soon be available

4.1.1. Factor VIII / Factor IX

In the case of life threatening haemorrhage infusion of factor VIII or factor IX in large doses can be used to swamp the inhibitor. This therapy is mostly used in patients with low responding inhibitors (inhibitor titre is <5 BU/mL after infusion of factor VIII). In patients who are high responders, this treatment may be effective for short periods of time provided the inhibitor level is less than 5 BU/mL. Factor VIII and factor IX levels should be observed to assess and monitor response. Anamnesis can occur 5-7 days after therapy and make factor VIII ineffective. Patients with factor IX inhibitors can experience allergic reactions upon re- exposure to factor IX and administration should only be given in the hospital setting with access to facilities to manage anaphylaxis.

4.1.2. Recombinant Factor VIIa

This product has been widely used in Australia and has proved to be highly effective in the management of bleeding episodes in patients with inhibitors to FVIII or FIX. Evidence in the literature suggests that it is effective in 79-92% of such episodes [4]. In addition, there is evidence that it is effective in over 90% of cases of surgery [4].

Recombinant factor VIIa is infused as a bolus. Continuous infusion of recombinant factor VIIa may reduce the quantity and cost of treatment but evidence is conflicting. A recent study suggests continuous infusion of 50 µg/kg/hr is effective in surgery [3]. Antifibrinolytics may be administered concurrently but may increase the risk of thrombosis in some patients. The standard adult dose of recombinant factor VIIa is 90 µg/kg. Doses may need to be repeated every 2– 3 hours until bleeding settles. Recent evidence suggests that larger doses (e.g. 270 µg/kg) maybe as effective as repeated doses of 90 µg/kg [5]. In children the mean half life is substantially reduced to 1.32 hours and thus higher doses of up to 200-250 µg/kg may be required.

Recently the use of rVIIa as secondary prophylaxis has been approved by the NBA. The regime of 90µg/kg daily for up to 3 months may be trialled in patients who experience a high incidence of bleeding (defined as four bleeds per month).

4.1.3. Activated Prothrombin Complex Concentrates (APCCs) eg FEIBA

Activated prothrombin complex concentrate, such as FEIBA, is effective in the treatment of 90% of bleeding episodes, and has been effective in the management of bleeding during major surgery [4]. An effective dose is 60-100 units/kg twice per day. The maximum daily dose of FEIBA is 200 units/kg/day. Antifibrinolytic agents, such as tranexamic acid, should not be administered concurrently with FEIBA. It should be noted that FEIBA contains small amounts of factor VIII and therefore may cause elevation of inhibitor titres in some patients.

In patients who are having frequent bleeds, a trial of FEIBA as prophylaxis may be considered. The suggested dose is 75-100 units/kg three times a week. FEIBA is not currently approved by the TGA for use as prophylaxis.

4.1.4. Prothrombinex-HT

Despite general scepticism about the effectiveness of prothrombinex-HT in the management of joint haemorrhage, some patients report benefit and continue to be treated with this product. There are concerns about the incidence of thrombosis when using repeated high doses, particularly in the presence of liver disease and when used in combination with antifibrinolytics. There is no evidence of efficacy in serious haemorrhages in surgery [2]. AHCDO recommends that recombinant factor VIIa or FEIBA is used in future for these patients. Prothrombinex contains factor IX and should be used in caution in patients who have inhibitors to factor IX and allergic reactions.

4.1.5. Antifibrinolytic therapy

Antifibrinolytic therapy is particularly effective for mucosal bleeding episodes. The recommended dose of tranexamic acid is 80-100 mg/kg/day, with a standard dose being 1g, *qid* given orally (recommended paediatric dose is 35 mg/kg/8hr). An intravenous preparation is available in Australia through the SAS. Intravenous epsilon aminocaproic acid (EACA) is no longer produced and not available.

4.1.6. Immunomodulation

A number of immunomodulation strategies, including plasmapheresis to reduce the inhibitor titre and allow treatment with FVIII, have been suggested for patients who with inhibitors to FVIII and FIX presenting with acute haemorrhage. Specific immunoabsorption using the Malmo protocol [5] is not available in Australia.

4.2. Treatment Regimens for control of haemorrhage

4.2.1. Low titre inhibitor (<5 BU/ml), low responder

The recommended dose of factor VIII is 50-100 IU/kg repeated every 8-12 hours. Doses of factor IX of 100 – 200 IU/kg 12 – 24 hourly may be used in patients with low titre factor IX inhibitors and no or limited allergic reactions to factor IX who present with bleeding.

4.2.2. Low titre inhibitor (<5 BU/ml) AND history of high responder

Infusions of factor VIII or factor IX will likely cause an anamnestic rise of the levels of factor VIII inhibitor within 3-5 days rendering further therapy with factor VIII or factor IX ineffective. Recombinant factor VIIa or FEIBA should be considered to manage bleeding episodes in these patients.

4.2.3. High titre inhibitor (>5 BU/ml)

Recombinant factor VIIa or FEIBA should be considered to manage bleeding episodes in these patients.

4.2.4. Elective Major Surgery

Major surgery in patients with inhibitors carries a high degree of risk and should only be carried out in recognised HTC's after careful consultation and agreement with at least one other Australian haemophilia specialist. The TAC can be utilised for this purpose. All such discussions should be documented. It is recommended that a pharmacokinetic study be undertaken before surgery. The dosage regimen is based on the regimen for major bleeds.

Dental surgery and the insertion of IV access devices require 3-5 days of therapy and antifibrinolytics.

4.2.5. Emergency Major Surgery

The dosage regimen is based on the regimen for major bleeds. If time allows, there should be consultation and agreement with one other haemophilia specialist as in Elective Major Surgery. Any such discussion should be

documented. The patient should be transferred to a recognised HTC as soon as practicable.

4.2.6. Home Therapy

AHCDO recommends that home therapy only be considered with close monitoring and regular medical supervision.

5. TOLERISATION

5.1. Haemophilia A

Tolerisation should be considered in all patients with inhibitors to factor VIII. Immune tolerance induction (ITI) is defined as eradication of an inhibitor by high dose antigen exposure with or without immune modulation therapy. Tolerisation is an active procedure that may involve development of antibodies against IgG factor VIII or factor IX antibodies. Intensive replacement therapy for immune tolerance usually requires central venous access.

Despite decades of experience with ITI, little information from scientific studies is available to guide clinicians in the management of ITI. The international ITI study which is a randomised trial between high dose therapy (200 units/kg/day) and low dose therapy (50 units/kg three times per week) was initiated in 2002 and will hopefully address a number of outstanding issues regarding ITI. Findings from an International Workshop on Immune Tolerance Induction have recently been published[3].

A number of international and national registries of tolerisation offer information on prognostic information for patients having ITI. In a meta-analysis of these registries, two predictors of success for ITI were identified; historical peak inhibitor titre and titre of inhibitor at initiation of ITI [3]. Based on this information and from an interim report from the International Immune Tolerance study [6], the following are noted

- Waiting for the inhibitor titre to fall to < 10 BU prior to commencement of ITI. The median delay between the development of an inhibitor and the drop off in titre is 6 months. (reference).

- In a patient who is considered good risk (low historical peak titre < 200 BU, < 5 years since diagnosis of inhibitor, pre ITI titre < 10 BU), participation in the International Immune Tolerance Trial is recommended.
- In a good risk patient who is unable to participate in the international trial, there is no information to guide clinicians in dose (high or low dose).
- There is no information to support the choice of particular factor VIII products in good risk patients and in general, the patient should be tolerised with the same product used at the time of developing an inhibitor
- In poor risk patients (historical titre > 200 BU, > 5 years from diagnosis, pre-ITI titre > 10 BU) evidence suggests higher dose regimes may be more successful (e.g. 200 IU/kg/day)
- Patients who show poor response to ITI (defined as showing a < 20% reduction in inhibitor titre for any 6 month period after the first 3 months of treatment) should be considered for second therapy. This includes changing to a FVIII product containing vWF or immune modulation such as anti-CD20 therapy.
- Successful ITI is defined as
 1. Negative inhibitor screen
 2. FVIII recovery of > 66% of predicted
 3. FVIII half life of > 6 hours after a 72 hour wash out period

5.2. Haemophilia B

ITI for patients with haemophilia B and inhibitors to FIX is difficult. Successful ITI in these patients is significantly less than in patients with haemophilia A. Additional allergic complications of anaphylaxis and development of nephritic syndrome in the setting of ITI is well described but poorly understood. Patients with large gene deletions of the FIX gene may be more at risk of developing this complication. There is limited information available to guide clinicians in the management of these patients. A number of scattered case reports describe the use of various forms of immune modulation to maximise the success of ITI in patients with haemophilia B.

No recommendations regarding ITI can be provided for patients with haemophilia B and inhibitors to factor IX. Patients who have ITI attempted should have regular assessments to exclude proteinuria and development of nephritic syndrome [3].

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