MANAGING PATIENTS WITH INHIBITORS

Alloantibodies to factor VIII occur in 10 - 15% of patients with classical haemophilia (usually <10% FVIII level) and usually within the first 25 treatment exposure days. Inhibitors do not occur after 200 treatment exposure days.
Factor IX antibodies are extremely rare.

INFORMATION REQUIRED

Titre of the factor VIII inhibitor at the time of therapy.

- $\leq$ 5 BU can be treated with neutralizing doses of Factor VIII
- 5 $\leq$ 20 BU may respond to neutralising doses of Factor VIII
- 20 BU/ml unresponsive to FVIII concentrate.

Is the patient known to have an inhibitor of the low or high responder type?

- Majority of patient (>75%) are high responders.
- A low responder antibody remains <5 BU/ml.

Severity and site of bleeding.

MANAGING ACUTE BLEEDS

Discuss with the Regional Haematologist for individual treatment plan.

FVIIa (Novo Seven) is the recommended initial therapy.
Use only at the direction of a specialist haematologist involved with haemophilia care.
FEIBA can be considered as an alternative.

Consider assessing the response to non-activated prothrombin complex concentrate (Prothrombinex). Few patients show response to this treatment and it should not be used in a newly diagnosed case. However some established cases do gain some benefit from this treatment for a minor bleed.

MINOR BLEEDS

Recombinant Factor VIIa (Novo Seven)

TREATMENT REGIMEN
Conservative measures and pain relief should be considered for very minor bleeds.
rFVIIa: Recommended initial dose of 90 µg/kg followed by a second dose at 2 hours.
Further doses may be required if there is evidence of continuing bleeding.

Prothrombinex for patients previously shown to respond to this treatment.

TREATMENT REGIMEN
Prothrombinex 50 - 100 u/kg for 3 doses then review.

MAJOR BLEEDS

TREATMENT REGIMEN

Recombinant factor VIIa (Novoseven)

Recommended dose of 90 µg/kg given 2 hourly initially, with frequency reduction to 3 hourly and then 4 hourly as indicated by clinical progress until bleeding ceases.

FEIBA

Factor Eight Inhibitor Bypassing Activity is an activated prothrombin complex concentrate available as FEIBA TM-4 (specific activity 0.7 - 2.5 units/mg) prepared from pooled human plasma and high heat treated (60^{o}C for 10 hours and 80^{o}C for 1 hour during production). FEIBA has been used to treat joint, muscle and soft tissue bleeding in patients with both high and low responder inhibitor titres where the antibody is $\geq$ 5 BU. It has also been used for life threatening bleeds and surgery.

Dosage schedules, independent of inhibitor titre, are between 50 - 100 u/kg repeated 6 - 12 hourly for patients with haemophilia. Lower doses given more frequently by intermittent infusion may be preferable in some circumstances. Doses of 20-60 units FEIBA/kg of body weight are given up to 8 hourly in non-haemophilia patients with spontaneous inhibitors. The total daily dose of FEIBA should not exceed 200 u/kg body weight per day.

Efficacy rates reported in clinical trials are 80-90%.

TREATMENT REGIMEN

Joint, Muscle and Soft Tissue Haemorrhage
Minor-moderate bleeds 50-75 u/kg 12 hourly.
Major muscle bleeds 100 u/kg 12 hourly.

Mucous Membrane Bleeding
50 U/kg 6 hourly with dose escalation to 100 u/kg if required.

CNS or Life Threatening Bleeds
100 u/kg 12 hourly. More frequent administration of lower doses at 2 - 4 hourly intervals should be considered in this setting.

Surgery
50-100 u/kg 6 hourly (up to maximum dose 200 u/kg per day).

LOW LEVEL INHIBITOR

Neutralising doses of Human FVIII C can be used in a patient with an inhibitor of less than 2.0 Bethesda units. The neutralising dose is usually 2-3 times the standard dose regimen.

Continuous infusion or intermittent dosing can be used.
Give initial test dose of approximately 100units. Have adrenaline and hydrocortisone near at hand.

TREATMENT REGIMEN

Initial bolus of 5,000 units of factor VIII followed by 500 - 1000 units hourly by continuous infusion (adults). Pro-rata reduction according to body weight in children.
Intermittent therapy is usually 25-100u/kg, depending on the indication.
Measure factor VIII level 3 hours after starting therapy.

Measurable factor VIII levels (>2 - 3%) should encourage continuation of therapy with the expectation that levels will continue to rise.

If levels are not measurable (0 - <1%) higher doses and continued infusion is unlikely to be effective.

When infusions are continued, maintain high levels and do not reduce infusion rate by more than 25% per day.

Monitor factor VIII levels daily. When factor VIII level starts to fall subsequent increases in the infusion rate are usually ineffective.

A reactive increase in antibody (anamnestic response) usually begins at 3 - 7 days peaking at 14 days. This will result in resistance to the infusion regime. Thrombocytopenia may occur.

Immune Tolerance Therapy (ITT)

AIM To suppress inhibitor by high dose repeated infusion of factor VIII concentrate.

There are a number of different regimen reported for ITT.

These generally use 50 - 200 u/kg once daily as the starting dosage.

There are no data for continuous infusion but, if the child is in hospital, it is theoretically advantageous to give the first dose as a bolus and then divide the daily dose as a continuous infusion to increase the time of antigen exposure to the T lymphocytes. Continuous infusion with or without recombinant FVIIa may be necessary to facilitate insertion of a portacath.

The best predictor of a successful outcome of ITT is a starting inhibitor titre $\leq$10 BU. Dosage of 50 - 100 u/kg/day initially seems to be most cost effective although German experts have recommended higher dosages. At present there is no evidence to show that the type of product used for ITT is an important variable.

The peak inhibitor titre and its duration may influence response. If the peak inhibitor titre is $\leq$50 BU, and the duration of the inhibitor <5 years, there is a predicted 90% or greater success rate with ITT. If the peak inhibitor titre is greater than 50 BU and duration greater than 5 years, the response rate is less than 50%.

Product choice will be either recombinant or plasma derived factor VIII depending on the individual meeting access criteria for recombinant therapy. At present there is no difference in outcomes between patients treated with recombinant or plasma derived factor VIII.

The Medical Advisory Committee of the NZ Haemophilia Foundation prepared the following algorithm.

<table>
<tr><td colspan="3">ELIGIBLE PATIENT

STARTING FVIII at a dose of up to 200 u/kg/day
(protocols using either 100u/kg or 200u/kg have been used)

Measure inhibitor titres (BU) every 2 to 4 weeks

↓</td></tr>
<tr><td colspan="3">Review at 3 months
Is the inhibitor titre <2.0 BU?</td></tr>
<tr><td colspan="2">Yes

reduce to 50 u/kg/day
measure inhibitor monthly</td><td rowspan="4">No

Repeat x 1
If already repeated this once i.e. 6 months of 100 u/kg/day and BU >2.0, refer to Medical Advisory Panel for review.

Likely to exit tolerance programme if very poor response.

If signs of falling titres then to continue on tolerance programme reducing to 50 u/kg/day with monthly BU.
Review by Panel at 12 months before going to low dose tolerance (equivalent to prophylaxis).</td></tr>
<tr><td colspan="2">Review at 6 months
is the inhibitor titre <2.0?</td></tr>
<tr><td>Yes
reduce to 25 u/kg/day for a further 8 weeks</td><td rowspan="2">No
continue with 50 u/kg/day for a further 6 months
If titre >2.0

If inhibitor titre remains >2.0 BU refer to Medical Advisory Panel</td></tr>
<tr><td>Titre remains <2.0 BU

prophylaxis of 20 - 25 u/kg/day 3 times a week</td></tr>
</table>

- Following initiation of I.T.T., weekly inhibitor assays are recommended to define the anamnestic response. This is useful to document the peak titre and the rate of fall in inhibitor titre of I.T.T. Inhibitor assays should be performed at a minimum of each month during the first three months and subsequently at a minimum of three monthly for the first 12 months.

- All dosage changes should be accompanied by recovery studies whenever possible.

- Transient rises in inhibitors can occur with an intercurrent inflammatory stimulus such as infection, other illness or a significant bleed.

Access Criteria:

- Applications for I.T.T. are made to the Tolerisation Advisory Committee through the Chairperson of the Medical Advisory Committee of the N Z Haemophilia Foundation.

- The patient must be under the direct care of a Regional Haemophilia Centre.

- Treatment must be approved by the Medical Advisory Committee

- Progress will be reviewed by the Medical Advisory Committee at least every 6 months.

Assessment

- In assessing priority for this therapy preference will be given to children ≤5 years, with a low titre (10 BU or less) and a short duration of inhibitor.

- The inhibitor titre must be confirmed on at least two occasions ≥7 days apart. A titre ≥5 BU defines a high responding inhibitor.
- It is important to ensure that patients with transient low titre inhibitors are not entered into an I.T.T. programme. These inhibitors are usually <1 - 2 BU.

- Factors to be considered in assessing suitability for entry into an I.T.T. programme include

  - the duration of the inhibitor.
  - maximal inhibitor titre.
  - titre immediately prior to initiation of I.T.T.
  - consideration of concomitant conditions especially where these may significantly limit life expectancy.
  - psychosocial assessment of patient and family to determine ability to cope with I.T.T. programme.
  - agreed cooperation and acceptance of I.T.T. therapy requirements by patient and/or parent/guardian. Written informed consent prepared.
  - acceptance by the patient (and/or family) for placement of an intravenous access device, the need for ongoing catheter maintenance, good infection control practice and replacement of the indwelling device if needed.

- Patients may be refused entry on any of the following criteria

  - inhibitor duration.
  - other morbidity.
  - patient/family's ability to comply with the regimen.

OUTCOME

At least six months of high dose therapy is needed for the inhibitor (BU) to fall to ≤2.0. Further therapy (six months or longer) may be necessary for complete suppression.

The criteria for successful immune tolerisation

- Absent or barely detectable inhibitory activity.
- Evidence of factor VIII recovery (30 minutes) post infusion.
- Factor VIII half-life ≥4 hours by fall off study.

Long term prophylaxis

- Following successful I.T.T., prophylaxis will be continued indefinitely (lifelong) to prevent inhibitor recurrence.
- Repeat recovery studies and antibody titres:-
  - three months after starting prophylactic dosing.
  - six monthly for two years.
  - annually beyond two years.

FAILURE OF I.T.T.

If by 12 months successful I.T.T. has not been achieved, the patient should be referred to the Medical Advisory Committee for careful review.

If at 12 months the inhibitor titre is equal to or greater than the starting titre, the I.T.T. programme would usually be regarded as having failed and the patient withdrawn from the programme.

Continued prophylaxis may be recommended by the Tolerisation Advisory Committee on an individual basis. Failure to comply with recommended treatment and support protocols may also be a reason for ceasing the I.T.T.

The Tolerisation Advisory Committee may therefore discontinue the I.T.T. regimen after 12 months based on the following:-

- persistently elevated inhibitor level with little evidence of response.
- other morbidity.
- patient/family's level of compliance unacceptable.

INTRAVENOUS GAMMAGLOBULIN (INTRAGRAM) (another potential inhibitor therapy)

1g/kg intravenously daily for two days, particularly consider for factor VIII autoantibodies.

IMMUNOSUPPRESSION:

Disappointing for alloantibodies; used in the management of autoantibodies.
Prednisone 1 mg/kg for three weeks, then taper.
Cyclophosphamide 2 -3 mg/kg orally initially then reducing to 0.75 - 1 mg/kg for 3-6 months. Alternatively, cyclophosphamide may be administered by the intravenous route initially as bolus injections of 1- 2 g on a weekly schedule.