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UKHCDO protocol for first line immune tolerance induction for children with severe haemophilia A:

A protocol from the UKHCDO Inhibitor and Paediatric Working Parties (1st February 2017)

Infants and children with severe haemophilia should be tested for an inhibitor at least every third exposure day (ED) until 20 EDs and subsequently every 3-6 months until 150 EDs to ensure that an inhibitor is detected and treated early. When an inhibitor is detected all cases should be offered Immune tolerance induction (ITI) in order to optimise the chances of inhibitor eradication.

Immune tolerance induction (ITI) must be coordinated by a Comprehensive Care Haemophilia Centre with expertise in ITI.

1. Indications for ITI

Children with severe haemophilia A and a factor VIII inhibitor, demonstrated on more than one occasion by a Nijmegen-modified Bethesda assay, that interferes with prophylaxis or treatment of bleeds at standard doses of FVIII.

These children should undergo ITI to eliminate the inhibitor and restore normal clinical responsiveness to FVIII.

2. Timing of ITI

ITI should be started as soon as an inhibitor is confirmed ***irrespective of the titre***.

3. Venous access

A central venous access device should be inserted if required to facilitate uninterrupted ITI.

4. Initial ITI regimens

First line ITI should be conducted using recombinant FVIII concentrate (unless as part of a clinical trial). This is usually with the product used by the patient at the time of inhibitor development.

Regimens are outlined below:

Historic peak inhibitor titre	Regimen
<5 BU	• Start ITI at a dose of 50 IU/kg on alternate days. • Escalate the frequency, then dose if necessary, to control haemarthroses and clinically significant breakthrough bleeds, initially using daily treatment and then increasing factor VIII dosage in increments of 50 IU/Kg/day up to 200 IU/kg/day. • If the inhibitor titre on this ITI regimen increases above 40 BU, increase dose immediately to 100 IU/kg/day. If the inhibitor titre increases above 200 BU increase the dose immediately to 200 IU/kg/day.
>5 and <200 BU	• Start ITI at a dose of 100 IU/kg/day. • Escalate the dose of FVIII, if necessary, to control haemarthroses and clinically significant breakthrough bleeds, by increments of 50 IU/Kg/day up to 200 IU/kg/day. • If the inhibitor titre rises to >200 BU, increase dose immediately to 200 IU/kg/day.
>200 BU	• Start ITI at a dose of 200 IU/kg/day.

The ITI doses should not be interrupted once started because this will compromise the success of ITI.

5. Monitoring ITI

The inhibitor titre should be measured weekly after initiation of ITI to define the peak inhibitor titre. A Bethesda assay with Nijmegen modification and no washout period should be used.

Once peak titre has been defined, the inhibitor titre should be monitored monthly thereafter. ITI should be continued as long as there is a sustained downward trend in inhibitor titre.

If there is an upward trend in titre, or inadequate reduction in titre over a 6 month period - defined as a fall in Bethesda titre of less than 20% in a 6 month period - modify the regimen:

- If factor VIII dosage <200 IU/kg/day, increase to this dose.
- If factor VIII dosage 200 IU/kg/day, change to second line regimen (see below).

NOTE: port a cath infection can cause an increase in inhibitor titre or a poor response to ITI and should be excluded before assuming an inadequate response.

6. Dose tapering when Bethesda is negative

Dose tapering should **not** be attempted in poor risk patients (titre at start of ITI >10 BU, peak titre on ITI >200 BU) until the FVIII half-life is greater than 7 hours and dose reduction should then be undertaken cautiously.

In good risk patients (titre at start of ITI <10 BU, peak titre on ITI <200 BU), when the Bethesda assay after heat treatment (58°C for 60 minutes) is negative for 2 consecutive months continue ITI regimen unchanged but perform the following measurements monthly;

- 24 hour trough factor VIII level
- *In vivo* recovery (IVR) (measured with a pre and a 15 minute post sample).

When 24 hour trough level is >1 IU/dL for 2 consecutive months dose reduction can be initiated;

- Reduce factor VIII dosage by available vial size increments, but maintain the 24 hour trough factor VIII level >1 IU/dL. If breakthrough bleeds occur, FVIII trough should be maintained at a higher level.
- To help guide dose tapering, the trough FVIII level is proportional to the dose if the half-life remains constant. Therefore if the dose is reduced by 50% the trough will also decrease by about 50%.
- The factor VIII dose should not be reduced by more than 50% at one time and the trough should be measured soon after the reduction to ensure a level above 1 IU/dL is maintained.

Continue to measure Bethesda titre and 24 hour trough factor VIII level monthly and reduce FVIII dose further if trough is >1 IU/dL.

- Maintain the 24 hour trough >1 IU/dL during dose reduction.
- If the Bethesda titre becomes positive, the 24 hour trough factor VIII level is <1 IU/dL, or a breakthrough bleed occurs, reintroduce the previous factor VIII dosage.
- When the factor VIII dose has been reduced to 50 IU/Kg/day and the 24 hour trough factor VIII level is >1 IU/dl, either continue daily infusions or switch to alternate day treatment. (Alternate day treatment is likely to require an increase in total factor VIII dose to maintain a 48 hour trough factor VIII level of > 1 IU/dl and pharmacokinetic studies will be helpful to plan the change in regimen).
- Continue to reduce factor VIII dose to maintain a 24 or 48 hour trough factor VIII level of > 1IU/dl and to prevent breakthrough bleeds.

7. Definition of tolerance

Standard half-life factor VIII

The child is considered tolerant when a post washout Nijmegen Bethesda is negative and FVIII half-life is >7 hours.

A surrogate measure of a FVIII half-life >7 hours is when the FVIII dose has been reduced to ≤50 IU/kg on alternate day and the trough FVIII level is ≥1 IU/dL.

Enhanced half-life factor VIII

The child is considered tolerant when a post washout Nijmegen Bethesda is negative and FVIII half-life is above the lower end of the normal range for children below the age of 6 years for the concentrate being used.

8. Partial remission

Partial remission is defined as Nijmegen Bethesda assay negative and trough FVIII level maintained >1 IU/dL on either daily or alternate day treatment, without fulfilling the additional half-life and/or dose reduction thresholds defining complete tolerance.

9. Follow up

Prophylaxis should be continued indefinitely.

- Monitor the Bethesda titre and trough factor VIII level monthly for 6 months, then 2 monthly for 12 months and then routinely.
- Restart ITI immediately if relapse detected.

10. Poor responders and second line therapy

If there is an inadequate sustained downward trend in the inhibitor titre (see section 5), consider alternative strategies;

- Options include FVIII dose increase, the introduction of plasma derived FVIII with a high vWF content (pdFVIII) or immunosuppression with rituximab.

Timelines for second-line therapy

- If there is no sustained downward trend after 6 months* of first line ITI, escalate to full dose (200 IU/kg/day)
- If there is no sustained downward trend after 6 months* of full dose ITI (200 IU/kg/day), change to pd FVIII or immunosuppression for a further 6 months*
    - NB; pd FVIII and and immunosuppression may be undertaken simultaneously or sequentially. If used sequentially and there is no downward trend after 6 months* with the 1st choice intervention, consider adding the alternate intervention with a further 6 months observation.

- If there is no sustained downward trend after 6 months of pd FVIII and immunosuppression and FVIII cannot be used to prevent and treat bleeds the ITI should be stopped.
- The final decision regarding cessation of ITI can be referred to a UKHCDO expert panel via the Inhibitor Working party Chairperson if uncertainty remains about interpreting response to 2nd line ITI strategies and/or future treatment planning with either FVIII concentrate or bypassing agents.

NOTE: time periods denoted by * indicate maximum time to wait before evaluation of response. Earlier changes can be made if the inhibitor titre is increasing or a sustained

11. ITI outcome

All ITI treatments and the outcome of each intervention must be reported to the National Haemophilia Database every 3 months.

Reference

Diagnosis and treatment of factor VIII and IX inhibitors in congenital haemophilia: (4th edition). A United Kingdom Haemophilia Centre Doctors' Organisation guideline approved by the British Committee for Standards in Haematology

Collins PW, Chalmers E, Hart DP, Liesner R, Rangarajan S, Talks K, Williams M, Hay CR. British Journal of Haematology 2012.