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Immune tolerance induction in severe haemophilia A: A UKHCDO inhibitor and paediatric working party consensus update

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Abstract

Introduction: In good risk patients (historic inhibitor peak < 200BU), the International Immune Tolerance Study demonstrated equal efficacy to induce tolerance between high (200iu/kg/day) and low dose (50iu/kg ×3 times/week) immune tolerance induction (ITI) regimens. However, the trial stopped early on account of the excessive bleed rate in the low dose ITI arm.

Methods: United Kingdom Haemophilia Centre Doctors' Organization (UKHCDO) Paediatric and Inhibitor working parties considered available ITI data alongside the bi-phenotypic antibody emicizumab (Hemlibra®) efficacy and safety data to develop a consensus guideline for the future UK ITI guideline.

Results: This revision of UKHCDO ITI guidance incorporates the recommendation to use emicizumab as a prophylaxis haemostatic agent to reduce bleeding rates and to facilitate low dose and reduced frequency of FVIII CFC for ITI in the majority of children.

Conclusion: This consensus protocol will facilitate future evaluation of ITI outcomes in the evolving landscape of haemophilia therapeutics and ITI strategies.

KEYWORDS
immune tolerance induction, FVIII, emicizumab, severe haemophilia A, tolerance, ITI, PUP

1 | INTRODUCTION

The haemophilia A treatment landscape continues to evolve, most recently with the pivotal trial completion and regulatory approval of the biphenotypic antibody, emicizumab (Hemlibra®, Roche) for both inhibitor and non-inhibitor settings.[1–3] United Kingdom Haemophilia Centre Doctors' Organisation (UKHCDO) believe long term FVIII tolerance induction and long term maintenance remains an important treatment goal for newly confirmed inhibitors in minimally treated patients (< 150exposure days (EDs)) and, thus, Immune Tolerance Induction (ITI) remains the recommended UK standard of care in this group. Prior to emicizumab approval, previous UKHCDO ITI guidance recommended moderate (100u/kg) and high (200u/kg) dose, high frequency(daily) FVIII concentrate use for high titre inhibitor ITI, recognizing the unacceptable high bleed rates in the low dose (50u/kg), low frequency arm of the international ITI study.[4,5] Now, using emicizumab as a concurrent prophylaxis agent, this revised UKHCDO ITI guidance aims to harness the observed equivalence of low and high dose FVIII to induce tolerance.[5] Low dose, less frequent FVIII dosing in this recommendation will offer a significantly less arduous ITI treatment regimen for the majority of parents without compromising the chances of achieving FVIII tolerance for their son.

2 | FVIII INHIBITOR SCREENING

If an infant or child has been commenced on FVIII clotting factor concentrate (CFC), inhibitor testing should remain as previous guidance: at least every third ED until 20 EDs and subsequently every 3–6 months until 150EDs to ensure that an inhibitor is detected and treated early. If an inhibitor is detected and confirmed, all cases should be offered ITI in order to optimize the chances of inhibitor eradication. Aiming to tolerise a boy with an inhibitor remains the national consensus management strategy.

If an infant or child has been commenced on emicizumab as the first prophylaxis agent, utilizing FVIII CFC for on demand treatment, inhibitor testing should be performed 2–6 weeks after every FVIII CFC treatment episode for the first 50EDs, then 3–6 monthly thereafter whether exposed to CFC or not in that period, as cases have been identified in the UK of inhibitors emerging in patients treated with emicizumab in the absence of recent FVIII exposure (personal communication, E Chalmers, Paediatric Working Party chair and UK National Haemophilia Database). If a treatment episode is intensive (3+ EDs), in vivo recovery (IVR) and inhibitor testing should be considered during the episode, particularly if the patient has not yet accumulated a lifetime exposure to CFC of > 20ED.

2.1 | Indications for ITI

ITI should be offered to children with severe haemophilia A and a factor VIII inhibitor > = .6BU, demonstrated on more than one occasion by a Nijmegen-modified Bethesda assay, ensuring bovine chromogenic reagents are utilized if emicizumab is present in the patient sample.

Families should be counselled about the value of long-term tolerance to FVIII CFC and rationale for ITI to eliminate the inhibitor and restore normal clinical responsiveness to FVIII.

2.2 | Timing of ITI initiation

ITI should be started as soon as an inhibitor is confirmed, irrespective of titre, without interruption to treatment in the case of those receiving FVIII prophylaxis. The inhibitor titre should be checked with a bovine chromogenic Bethesda assay even if emicizumab has yet to be started to ensure the continuity of titre interpretation if emicizumab is subsequently commenced.

3 | Venous access

A central venous access device should be inserted if required to facilitate uninterrupted ITI. However, in contrast to previous guidance, ITI is likely to be Monday, Wednesday, Friday, or every other day (EOD) FVIII infusions for the majority and this may avert the need for a Port-a-Cath in some.

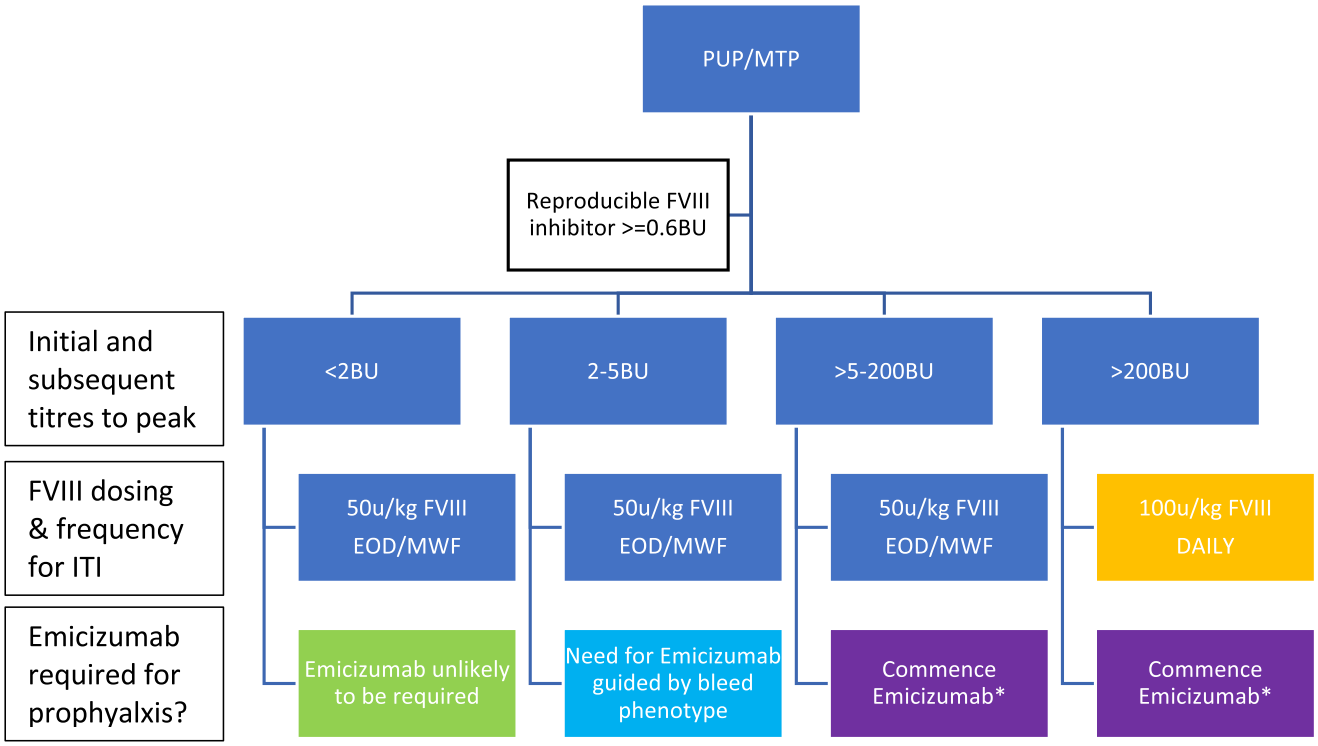

FIGURE 1 Initiation of Immune Tolerance Induction (ITI) in a minimally treated paediatric patient with severe haemophilia A and reproducible FVIII inhibitor > = .6BU. PUP, previously untreated patient; MTP, minimally treated patient; BU, Bethesda Unit; EOD, every other day; MWF, Monday, Wednesday, Friday; *Emicizumab loading and maintenance dosing should follow the accompanying manufacturer summary of product characteristics (SPC)

3.1 | Initial ITI regimens

First line ITI should be conducted using recombinant FVIII concentrate. In the absence of current high-quality data to demonstrate superiority of any one product, this is usually with the product used by the patient at the time of inhibitor development. If new, robust data emerges that a particular FVIII CFC preparation has enhanced efficacy in inducing tolerance, this should be considered as first choice.

Regimens as outlined below and illustrated in Figure 1:

3.1.1 | Inhibitor titre < 2 BU

If the infant or child had been started on FVIII CFC as first choice prophylaxis agent, then start ITI by increasing the FVIII dose to 50iu/kg EOD or Monday/Wednesday/Friday (if necessary to avoid port). If the peak titre remains < 2 BU and no breakthrough bleeds occur, emicizumab prophylaxis is not required. If a joint or clinically significant soft tissue bleed occurs requiring acute CFC treatment, then emicizumab should be started for future prophylaxis. Emicizumab loading and maintenance dosing should follow the accompanying manufacturer summary of product characteristics (SPC). Dosing frequency for maintenance emicizumab remains at the prescriber's discretion.

3.1.2 | Inhibitor titre 2–5 BU

Start low dose (50iu/kg Monday/Wednesday/Friday or EOD) immune tolerance.

The patients may or may not require emicizumab prophylaxis. Consider bleed phenotype and trend direction of the inhibitor titre to guide introduction of emicizumab. If the infant or child has already started emicizumab, then ITI should be commenced as above.

3.1.3 | Inhibitor titre > 5–200 BU

Start low dose (50iu/kg Monday/Wednesday/Friday or EOD) immune tolerance.

Concurrently, initiate emicizumab prophylaxis as per SPC guidance if this has not already been commenced.

Escalate the FVIII dose to 100iu/kg/day if the inhibitor titre on this ITI regimen increases above 200BU.

3.1.4 | Inhibitor titre > 200BU

Start ITI at 100iu/kg/day

Concurrently initiate emicizumab prophylaxis as per SPC guidance if not already commenced.

Break through bleeds should be treated according to UKHCDO guidance.[6]

ITI FVIII doses should not be interrupted once started as this may compromise the success of ITI.

3.2 | Monitoring ITI

The inhibitor titre should be measured weekly after initiation of ITI to define the peak inhibitor titre. A Bethesda assay with a Nijmegen modification and no washout period should be used. If the child was previously on (within last 6 months), remains on, or is being initiated on emicizumab, laboratory staff must be informed to ensure FVIII inhibitor levels are measured using chromogenic reagents containing bovine FIXa and FX components.[7] FVIII activity and FVIII inhibitor estimation should not be measured by one stage clotting assay in patients being treated with emicizumab, as the result is uninterpretable and invalid.[7]

Once the peak titre has been defined, the inhibitor 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 chromogenic Bethesda titre of less than 20% in a 6 month period, modify the regimen as below.

- If factor VIII dosage < 100 IU/kg/day, increase to this dose
- If factor VIII dosage 100 IU/kg/day, continue at this dose for a further 6 months (i.e. a complete 12 months at 100u/kg/day).

Escalation to daily treatment is likely to require a Port-a-Cath insertion.

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 tolerising response.

As Bethesda assays approach negativity, if patients are on emicizumab *and* 100iu/kg/day FVIII dosing, check in vivo recovery (IVR) (15 min after FVIII administration), to ensure peak FVIII:C levels do not rise > 150iu/dl on a regular basis, particularly in the presence of a port-a-cath, in order to reduce potential risk for thrombosis. In the event of peak FVIII:C levels > 150iu/dl, decrease FVIII dose to maintain a peak < 150iu/dl.

3.3 | Dose tapering when Bethesda negative

When the Bethesda assay becomes negative for the first time, check IVR again to avoid FVIII peaks > 150iu/dl, decreasing FVIII dose if necessary to maintain peaks < 150iu/dl.

When the Bethesda assay is negative for two consecutive months, perform the following measurements monthly:

- IVR (pre and 15 min post samples) to ensure FVIII peaks maintained < 150iu/dl, decreasing FVIII dose if necessary to maintain peaks < 150iu/dl
- 24 h trough FVIII:C level

When 24 h trough level is > = 2iu/dl, for 2 consecutive months, dose reduction can be initiated:

Reduce FVIII dosage by available vial size increments, but maintain the 24 h trough level > 1iu/dl.

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 50%

The factor should not be reduced by more than 50% at one time and the 24 h trough should be measured soon after dose reduction to ensure a level above 1iu/dl is maintained.

Continue to measure Bethesda titre and 24 h trough levels monthly and reduce FVIII dose further if trough FVIII:C is > 1iu/dl.

Maintain the trough > 1iu/dl during dose tapering.

If the Bethesda titre becomes positive or the 24 h trough drops < 1iu/dl, reintroduce the previous FVIII dosage.

If breakthrough bleeds occur whilst on emicizumab as prophylaxis agent during ITI, check compliance and consider investigation for emicizumab anti-drug antibodies (ADA) (see section 3.7).

When the factor VIII dose has been reduced to 50 IU/kg/day and the 24 h trough is > 1iu/dl, switch to alternate day treatment. Initially, this may require an increase in FVIII dose to maintain a measurable 48 h trough. At this point of achieving tolerance, emicuzimab should no longer be required as bleed prophylaxis. The decision of when to stop emicuzimab should be individualized to the patient and should be directed by the absence of breakthrough bleeds.

If possible dose reduce FVIII further whilst maintaining a measurable trough at 48 h.

3.4 | Successful tolerance

3.4.1 | Standard half-life FVIII

A patient is considered tolerant when a post washout Nijmegen Bethesda is negative and a FVIII half-life is > 7 h.

A surrogate measure of a FVIII half-life > 7 h is when the FVIII dose has been reduced to ≤ 50 IU/kg on alternate days and the 48 h trough FVIII level is ≥1iu/dl.

3.4.2 | Extended half-life FVIII

A patient 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, or for the age of the child undergoing ITI, for the concentrate being used.

3.4.3 | Tolerance maintenance

Once tolerance is achieved, FVIII CFC should be continued as prophylaxis to maintain tolerance. It is known that cessation of FVIII CFC and the use of emicizumab for prophylaxis carries a risk of inhibitor relapse (as occurred in the only patient in HAVEN 3 with previous ITI).[3] Although studies are underway to further understand this risk, it is not currently known how high that risk is. Consequently, the current UK consensus view is that post-ITI prophylaxis should be with FVIII CFC.

However, if families are unable to cope with FVIII prophylaxis and are adamant that they would prefer emicizumab, despite the potential relapse risks, there may be some merit in using a low dose FVIII regimen to try to maintain whatever level of tolerance has been achieved. This would need to be at a dose of ≤30iu/kg once a week to justify concurrent use of emicizumab *and* FVIII CFC. It should be emphasized that there is currently no evidence to support this approach and outcomes should be carefully monitored to inform future practice.

In this scenario, it is suggested that the dose of FVIII is de-escalated gradually to test whether tolerance is sufficiently robust to be maintained with a single FVIII CFC dose per week.

If a measurable 48 h FVIII trough is reproducible with a ≤ 50u/kg FVIII dose over 2 consecutive months, the dosing interval can be increased to every 72 h. Troughs will no longer be measurable at 72 h for SHL and may not be for EHL, but 48 h troughs and Bethesda assays should be measured monthly for 3 months as markers of continued tolerance. If the 48 h trough remains measurable and BU negative, dosing frequency should be further de-escalated to twice a week for 3 months with the same surveillance and then if tolerance maintained to once a week.

Once a patient is at once a week dosing, with a measurable 48 h trough and negative Bethesda assay with < = 50iu/kg, they should be maintained on weekly dosing (< = 30iu/kg) whilst continuing emicizumab as the primary prophylaxis agent. There is currently no evidence for a minimum dose required to maintain tolerance. Careful surveillance of tolerance maintenance should be undertaken monthly for 3 months, then quarterly in the first year and then a minimum of 6 monthly in the subsequent years.

3.5 | Partial tolerance

A patient will be considered partially tolerant to FVIII if he is able to use FVIII CFC as the primary prophylaxis agent to satisfactorily prevent spontaneous bleeds, treat trauma, and cover procedures and surgery safely, but does not fulfil the criteria for full tolerance. In this scenario, the family and patient should be re-counselled about the importance of maintaining FVIII tolerance with regular FVIII infusions to enable successful treatment of bleeds and trauma or cover surgery using FVIII.

If FVIII is stopped in a state of partial tolerance the risk of inhibitor recurrence is likely to be high. Children, particularly those who are on alternate day FVIII, should ideally continue with FVIII to maintain tolerance. Discussion at a national Multi-Disciplinary Team (MDT) may be helpful when making decisions about withdrawing ITI in patients who are partially tolerant.

Where treatment is daily and requiring very high dose FVIII it may be reasonable to consider switching to emicizumab acknowledging the high risk of inhibitor recurrence.

Treatment is likely to have to be individualized based on FVIII requirements, duration of ITI, patient choices/preferences.

3.6 | ITI failure

Failure of ITI is defined as the inability to utilize FVIII CFC as the primary prophylaxis agent to satisfactorily prevent spontaneous bleeds, treat trauma and cover procedures and surgery safely.

Failure of ITI would necessitate stopping FVIII concentrate, continuing or re-initiating emicizumab as primary prophylaxis and utilizing available BPA on demand to treat injury/bleed or cover surgery as per published UKHCDO guidance.[6] FVIII CFC may become an option for on demand use if/when the inhibitor titre declines into low titre range.

Clinician and family/patient discussion will be required to consider 2nd line therapeutic tolerance induction options which may include FVIII CFC product switch or immunomodulation (*e.g.*, anti-CD20 mAb, Rituximab). Given the availability of an efficacious prophylaxis agent in the presence of a chronic inhibitor,[1,2] and absence of robust data to support these 2nd line interventions, it is thought unlikely 2nd line agents will be used other than in exceptional circumstances. In such circumstances, discussion and agreement should be sought and documented after a convened MDT, including UKHCDO inhibitor and paediatric working party chairs and other member(s).

3.7 | Emicizumab anti-drug antibody (ADA) screening

Clinical teams should be mindful of the possibility of ADA directed against emicizumab, particularly in the event of breakthrough bleeding. Although clinically meaningful emicizumab ADA are thought to occur in < 2% of cases, APTT and emicizumab level monitoring will aid interpretation if clinical concerns.[8] Poor compliance remains the most likely explanation for dropping/low emicizumab level and breakthrough bleeding can occur despite good compliance and satisfactory emicizumab levels.[3] However, any combination of: dropping emicizumab levels; lengthening APTT; breakthrough bleeding of concern or no obvious explanation should prompt consideration of ADA screening. It is currently not necessary to routinely screen for emicizumab ADA in the absence of clinical concern

3.8 | Prospective data collection

UKHCDO and the National Haemophilia Database continue to collect prospective ITI and adverse event data. UK centres undertaking ITI will

be expected to continue to contribute tolerance monitoring data quarterly to the NHD.

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DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analysed in this study.

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