



Clinical Commissioning Policy Proposition: Immune Tolerance Induction (ITI) for haemophilia A (all ages)

Reference: NHS England F02X04/01

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**Clinical Commissioning Policy Proposition:
Immune Tolerance Induction (ITI) for haemophilia A (all ages)**

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Equality Statement

NHS England has a duty to have regard to the need to reduce health inequalities in access to health services and health outcomes achieved as enshrined in the Health and Social Care Act 2012. NHS England is committed to fulfilling this duty as to equality of access and to avoiding unlawful discrimination on the grounds of age, gender, disability (including learning disability), gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, gender or sexual orientation. In carrying out its functions, NHS England will have due regard to the different needs of protected equality groups, in line with the Equality Act 2010. This document is compliant with the NHS Constitution and the Human Rights Act 1998. This applies to all activities for which NHS England is responsible, including policy development, review and implementation.

Plain Language Summary

Immune tolerance induction is routinely commissioned by NHS England. This policy proposition reconfirms NHS England's commissioning approach to immune tolerance induction (ITI) in the treatment of Haemophilia A in adults and children with the aim of ensuring consistent, evidence based care.

Haemophilia A is an inherited condition, affecting predominately males, in which there is excessive bleeding which can follow trauma or occur spontaneously due to insufficient production of factor VIII, an essential blood-clotting protein.

Most people with severe haemophilia A require regular treatment with factor VIII in order to prevent bleeds. Some patients will form antibodies against the factor VIII, known as inhibitors. These inhibitors neutralise the circulating factor VIII, making it ineffective in preventing or stopping bleeds.

Immune tolerance induction (ITI) is the only proven method for eradicating inhibitors and involves administering factor VIII in increased doses, so that the immune system learns to tolerate the factor VIII, and ceases to produce inhibitors. It is important to begin ITI therapy as soon as inhibitors are identified and therefore it is predominantly a treatment option for very young children.

When successful, ITI allows factor VIII treatment to recommence at normal doses, preventing recurrent bleeding and progressive joint damage, and avoiding potential long-term implications of poorly controlled bleeds. The United Kingdom Haemophilia Centre Doctors' Organisation (UKHCDO) has developed a protocol for ITI in children.

NHS England has concluded that there remains sufficient evidence to support the routine commissioning of Immune Tolerance Induction (ITI) for patients who meet the proposed clinical criteria.

1. Introduction

Immune Induction Therapy is routinely commissioned by NHS England and is the only proven method for the eradication of inhibitors. This document reconfirms that NHS England will routinely commission ITI and sets out the proposed criteria for commissioning, proposed governance arrangements and proposed funding mechanisms.

For the purpose of consultation NHS England invites views on the evidence and other information that has been taken into account as described in this policy proposition.

A final decision on the adoption of this policy is planned to be made by NHS England by June 2016 following a recommendation from the Clinical Priorities Advisory Group.

2. Proposed Intervention and Clinical Indication

Haemophilia is an inherited genetic condition of which there are two main forms. The most common is Haemophilia A, a deficiency of coagulation factor VIII, which causes increased bleeding and usually affects males with a prevalence of between 1:5,000 and 1:10,000 in males. Recurrent bleeds lead to progressive joint damage and other complications.

Diagnosis would normally be made in early childhood and individuals diagnosed with severe haemophilia A require prophylactic treatment with recombinant factor VIII in order to prevent bleeds. Up to 30% of individuals with severe haemophilia A will form antibodies against administered factor VIII after commencing treatment. These antibodies are known as inhibitors. The inhibitors neutralise the circulating factor VIII, causing it to be broken down and removed from the blood stream. The level of risk of developing inhibitors to factor VIII depends upon the specific inherited genetic mutation, and this will vary from family to family. Generally speaking, the risk is higher in individuals with severe haemophilia, and usually occurs within the first 10-20 exposure days to administered factor VIII. However, inhibitors can develop even after many years of treatment.

To control bleeding, patients with inhibitors have to be treated with agents which bypass it. The two principle products available for this are recombinant factor VIIa (rFVIIa, Novoseven) and factor VIII bypassing agent (FEIBA). Both of these products are very expensive, and are not as effective as factor VIII in preventing bleeding.

Immune Tolerance Induction (ITI), also known as Immune Tolerance Therapy (ITT), involves administration of factor VIII in increased doses so that the individual's immune system learns to tolerate the factor VIII and ceases to produce inhibitors. The cost of a full course of treatment is considerable because the amounts of factor VIII used in ITI are relatively large. If successful, however, ITI reduces the risk of bleeds, joint damage and other complications.

Factor VIII is licensed for the treatment of haemophilia but the licence does not specify dosage or duration of treatment. The United Kingdom Haemophilia Centre Doctors' Organisation (UKHCDO) protocol for ITI in children sets out the dose and duration regimes tailored to patient specific needs.

3. Definitions

Haemophilia A is an inherited condition, affecting predominately males, in which there is excessive bleeding which can follow trauma or can occur spontaneously due to insufficient production of factor VIII, an essential blood-clotting protein.

Factor VIII is an essential blood-clotting protein leading to cessation of bleeding and clot formation following bleeding due to trauma and surgery.

An inhibitor is an antibody produced by the immune system which neutralises and de-activates factor VIII.

Immune tolerance induction (also known as immune tolerance therapy) is the administration of regular doses of factor VIII, with the aim of re-educating the immune system so that it no longer produces inhibitors in response to administered factor VIII.

The amount of inhibitor titres is measured in Bethesda units (BU). The higher the number of Bethesda units, the more inhibitors are present.

4. Aim and Objectives

This policy proposition aims to define NHS England's commissioning position on Immune Tolerance Induction (ITI) as part of the treatment pathway for adults and children with haemophilia A and inhibitors to factor VIII.

The objective is to ensure evidence based commissioning for adults and children with haemophilia A and inhibitors to factor VIII.

5. Epidemiology and Needs Assessment

There is no ethnic predominance for haemophilia A. Severe haemophilia A (factor levels less than 1%) represents approximately 35% of cases, moderate (factor levels of 1-5%) represent approximately 9% of cases and mild (factor levels greater than 5%) represent approximately 56% of cases (2013/14 UKHCDO register).

The overall prevalence of inhibitors in unselected haemophiliac populations has been found to be around 5-7%. Incidence and prevalence are substantially higher (12-13%) in patients with severe haemophilia. (Wight J. and Paisley S. The epidemiology of inhibitors in haemophilia A: a systematic review. Haemophilia 2003).

Incidence data are more appropriate in estimating the level of need for ITI, whereas the best estimates of the overall burden to the National Health Service (NHS) of treating bleeding episodes in patients with continuing inhibitors come from prevalence studies.

There were 2,034 patients with severe haemophilia A on the UKHCDO register in 2014/15. Of these around 21% (435) have ever had an inhibitor and around 8% (169) still have an inhibitor.

There are 531 patients with moderate haemophilia A on the 2014/15 UKHCDO register. Of these around 9% (49) have ever had an inhibitor and around 5% (24) still have an inhibitor.

Most patients who develop inhibitors do so within the first 10-20 treatments and therefore immune induction therapy is predominantly relevant to young children following diagnosis. About 25-30% of children with severe haemophilia A develop inhibitors.

6. Evidence Base

In considering the evidence, and in the context of the clinical consensus, NHS England has concluded that there is sufficient evidence to support a proposal for the routine commissioning of Immune Tolerance Induction (ITI) for patients who meet the agreed clinical criteria.

The evidence review sought to answer two questions:

1. What is the evidence for the clinical effectiveness of ITI for patients with haemophilia A who have developed inhibitors to factor VIII?
2. What is the evidence for the cost-effectiveness of ITI for patients with haemophilia A who have developed inhibitors to factor VIII?

A summary of the responses to the two questions is contained below:

Question 1: What is the evidence for the clinical effectiveness of ITI for patients with haemophilia A who have developed inhibitors to factor VIII?

Evidence from one RCT suggests that there are no significant differences in the ITI success rates between high-dose and low-dose FVIII regimens in paediatric patients with haemophilia A who have developed inhibitors and have an expected favourable response to ITI. These results are applicable to this patient group however; it is unclear if they would be valid in patients with risk factors associated with poor ITI prognosis. We also found some evidence to suggest that ITI with high-dose FVIII may be associated with fewer bleeding episodes; the RCT was stopped early because of safety concerns as there were significantly more bleeding events in the low-dose arm compared to the high-dose arm. Uncontrolled studies suggest that ITI has beneficial effects on patients with haemophilia A who have developed inhibitors. It is hard to gauge the extent to which these results can be attributed to ITI, or might have occurred spontaneously, but the studies are certainly compatible with a treatment effect. Retrospective analyses also tend not to document failures, so this could also have exaggerated the effect size in retrospective studies.

No studies were identified comparing ITI with alternative treatment schemes.

Question 2: What is the evidence for the cost-effectiveness of ITI for patients with haemophilia A who have developed inhibitors to factor VIII?

There is evidence from one UK conducted economic analysis in 2003 which suggested that the Malmo protocol as being the most cost-effective ITI regimen. The sensitivity analysis carried out also concluded that low dose ITI is likely to be the most cost-effective ITI

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regimen in the UK compared to on-demand therapy. However as the analysis was carried out in 2003, the relative costs and treatment strategies are likely to be out of date. In fact evidence from one RCT shows that low dose ITI is associated with significantly more bleeding compared with high dose ITI and this will not only reduce the patients' quality of life, it is likely to increase the costs because of the use of bypassing agents for the treatment of bleeds.

7. Proposed Criteria for Commissioning

NHS England will routinely commission ITI for the eradication of factor VIII inhibitors where the patient:

i. Is aged <19 years of age and has severe haemophilia A

AND

ii. Has a factor VIII inhibitor confirmed on more than one occasion by a Nijmegen-modified Bethesda assay, that compromises the effect of prophylaxis or treatment of bleeds at standard doses of FVIII

AND

iii. in the rare cases where a young adult patient previously treatment naive develops inhibitors soon after exposure to exogenous Factor VIII

Starting Criteria:

Where these criteria are met, ITI should be considered and started as soon as an inhibitor is confirmed irrespective of the titre.

Stopping criteria:

For good responders (estimated 75% of patients):

- Patients should continue on ITI with monitoring to detect the peak inhibitor titre and the downward trend in level.
- When the titre becomes negative dose tapering should be followed.
- The ITI is considered successful once the patient is on prophylaxis doses (≤ 50 U/kg alternate days) with a FVIII level of ≥ 1 iu/dl.

For poor responders (25% of patients):

- 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 and / or immunosuppression for a further 6 months.
- 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 ITI should be stopped.

(N.B. time periods indicate maximum time to wait before evaluation of response. Earlier changes can be made if the inhibitor titre is increasing or a sustained downward trend is unlikely).

Exclusion Criteria for ITI

- i. Individuals aged 19 and over (unless they are previously treatment naive young adults and develop inhibitors shortly after commencing exogenous Factor VIII)

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- ii. Patients not treated in accordance with a recognised protocol such as the UKHCDO protocol (children only)
- ii. Patients without confirmation of factor VIII inhibitor
- iii. Patients with haemophilia A who have had long standing inhibitors (over two years) and/or
- iv. Individuals with haemophilia A who have previous failed attempts at immune tolerance induction.

Given the nature of this condition and the above criteria, ITI will predominantly be initiated in young children following diagnosis and the instigation of treatment. Clinicians will be expected to adopt a recognised protocol such as the UKHCDO guidelines developed to ensure consistent, evidence based practice across England (<http://www.ukhcdo.org>). The lowest possible dose should be used to ensure adequate safety and effectiveness, with dosing tailored to ensure the most clinically and cost effective and optimal outcomes for the individual patient.

8. Proposed Patient Pathway

Infants and children with severe haemophilia (and adults who are initiating treatment) 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 immune tolerance induction (ITI) should be considered as an option to optimise the chances of inhibitor eradication.

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

For children, treatment should be undertaken in line with the UKHCDO protocol which reflects the UK clinical consensus on the optimal ITI treatment regime for children under the age of 18 (<http://www.ukhcdo.org>).

Where there is an inadequate sustained downward trend in the inhibitor titre, the specialist team would be expected to consider alternative strategies.

9. Proposed Governance Arrangements

Patients with FVIII inhibitors must be registered with, and have their treatment co-ordinated by a Haemophilia Comprehensive Care Centre experienced in the management of inhibitors and with expertise in ITI in accordance with the 2013/14 NHS Standard Contract for Haemophilia (all ages).

Individual treatment plans should be designed using a recognised clinical protocol.

In line with the NHS England service specification for specialised haemophilia services, centres must provide 24 hour access to senior clinicians with experience in inhibitor

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management and laboratory services for the measurement of factor levels and inhibitor titres.

Patients should be offered inclusion in appropriate clinical trials.

10. Proposed Mechanism for Funding

Funding for the clotting factor products required for ITI would be through the local NHS England specialised commissioning teams.

11. Proposed Audit Requirements

All patients must be registered with the National Haemophilia Database and details of their inhibitor reported as soon as they are confirmed. The outcome of ITI intervention must be reported to the National Haemophilia Database every 3 months.

All Haemophilia Comprehensive Care Centres will be required to participate in national audits, which will include:

- starting dose and dose changes to review compliance with protocols
- inhibitor titre levels
- partial and complete tolerance
- FVIII and bypassing agent usage

12. Documents That Have Informed This Policy Proposition

Clinical Commissioning Policy: Immune Tolerance Induction for children with severe haemophilia A and inhibitors to factor VIII, February 2014

Immune Tolerance Induction for patients with severe haemophilia A and inhibitors of factor VIII, Solutions for Public Health Evidence Summary Report, 2015

UKHCDO protocol for first line immune tolerance induction for children with severe haemophilia A, November 2015

13. Date of Review

This document will lapse upon publication by NHS England of a clinical commissioning policy for the proposed intervention that confirms whether it is routinely or non-routinely commissioned (expected by June 2016).