IMMUNE TOLERANCE INDUCTION FOR PATIENTS WITH SEVERE HAEMOPHILIA A AND INHIBITORS OF FACTOR VIII

QUESTIONS TO BE ADDRESSED:

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

SUMMARY:

Background

- Haemophilia A is the most common severe form of inherited bleeding disorder and is due to a deficiency of factor VIII (FVIII). Haemophilia A has an estimated incidence rate of 1 per 5,000 live male births. FVIII activities below 1% of normal are classified as severe, 1 to 5% as moderate and 5 to 25% as mild disease.
- The current treatment for haemophilia is replacement therapy, where the missing clotting factor is injected into the blood. The most serious complication in the treatment of haemophilia A is the development of antibodies against FVIII (inhibitors), causing therapy resistance and increased risk of bleeding. Up to 30% of patients with severe haemophilia A develop antibodies to factor VIII.
- A proportion of these antibodies disappear; antibodies cleared within 6 months are known as 'transient' while those lasting longer are called 'persistent' and are likely to continue throughout the patient's life.
- The approaches commonly used to treat patients with inhibitors are administration of bypassing agents[a] when a bleed occurs (on-demand), administration of bypassing agents prophylactically to prevent bleeds from occurring and initiation of immune tolerance induction (ITI) with FVIII concentrate to eradicate the inhibitor followed by long-term maintenance with a lower dose FVIII prophylaxis regimen to prevent a bleed and to sustain the inhibitor-free status.
- ITI is currently the only proven method for eradication of inhibitors but there is no consensus regarding the specifics of ITI treatment.

Clinical Effectiveness

- We identified two systematic reviews assessing the effects of immune tolerance induction (ITI) for treating inhibitors in people with congenital haemophilia A. We also identified one prospective observational study and one retrospective study published subsequent to the systematic review; both were uncontrolled.

[a] Bypassing agents are agents that are able to bypass the factor VIII–dependent step in the clotting cascade and promote haemostasis by enhancing thrombin generation.

- The first systematic review only included uncontrolled trials. The authors state that most of the studies reported 70 to 80 percent success, (complete or partial)[b] but with no direct comparators it is difficult to draw any conclusions.
- The second review, from the Cochrane Collaboration, included one randomised controlled trial (RCT). The RCT randomised 115 paediatric participants with severe haemophilia A receiving a first attempt at ITI to either low dose (50 IU/kg of factor VIII concentrate three times per week) or a high dose (200 IU/kg of factor VIII daily).
- The trial did not show any statistically significant difference in the success of ITI between treatment arms. However, the trial was underpowered and did not exclude a material difference in outcome between the treatments. The low-dose arm had significantly more bleeding than the high-dose arm but again the confidence intervals were very wide.

Cost Effectiveness

- We found three economic evaluations of ITI for patients with haemophilia A who have developed inhibitors of factor VIII.
- All the studies suggest that ITI is cost-effective compared to prophylaxis and on-demand treatment with bypassing agents. However the analyses were based mostly on low quality clinical evidence.

Safety

- Central venous access device (CVAD) infection was the most common complication observed in children with severe haemophilia A and inhibitors treated with ITI in the randomised trial. A total of 124 CVAD infections were reported in 41 of 99 (41%) subjects with an overall infection rate of 0.94 per 1000 CVAD-days. A similar number of infections were observed in the two treatment arms. Infections occurred more frequently in the presence of external catheters than with fully implanted catheters. ITI outcome was unaffected by CVAD infections.
- Other adverse events reported include haemarthrosis, febrile convulsion, gingivitis and allergic reaction to FVIII.

1 Context

1.1 Introduction

Haemophilia A is the most common severe form of inherited bleeding disorder, and is due to a deficiency of a clotting factor protein, factor VIII (FVIII).[1] Individuals with severe haemophilia A are typically diagnosed at an early age (usually in infancy) and have <1% of normal FVIII coagulant activity. FVIII activities between 1 to 5% are classed as moderate and 5 to 25% mild. [2] The current treatment for haemophilia A is replacement therapy with FVIII. The most serious complication of treatment for those with severe haemophilia A is the development of FVIII antibody inhibitors.[2, 3] A proportion of these antibodies disappear; antibodies cleared within six months are known as 'transient' while those lasting longer are called 'persistent' and are likely to continue throughout

[b] Complete success is defined as having undetectable inhibitor titre [<0.6 Bethesda Units (BU)] at 33 months of ITI, FVIII recovery ≥66% and half-life ≥7 h; partial success is defined as having a reduction in inhibitor titre to <5 BU per mL with FVIII recovery <66% and/or FVIII half-life <6 h associated with clinical response to FVIII therapy not followed by a treatment-limiting anamnestic rise in inhibitors to >5 BU per mL.

the patient's life although spontaneous clearance of inhibitors after six months has also been reported. [4]

Antibody inhibitors to FVIII are associated with increased mortality and significant morbidity, including a higher rate of bleeding complications, increased disability and decreased quality of life. [5-7] Three approaches are commonly used to treat such patients with inhibitors: (i) administration of bypassing agents[c] when a bleed occurs (on-demand), (ii) administration of bypassing agents prophylactically to prevent bleeds from occurring; or (iii) initiation of immune tolerance induction (ITI) also referred to as immune tolerance therapy with FVIII concentrate to eradicate the inhibitor followed by long-term maintenance with a lower dose FVIII prophylaxis regimen to prevent bleeds and sustain the inhibitor-free status. [7-9] ITI is currently the only proven method for eradication of inhibitors but there is no consensus regarding the specifics of ITI treatment. The most commonly used regimens in the UK are those recommended in the guidelines produced by the United Kingdom Haemophilia Centre Doctors' Organisation (UKHCDO) working group[10] (the Bonn protocol (high-dose FVIII) and the low-dose Van Creveld regimen (low dose FVIII)).

1.2 Existing national policies and guidance

We found no guidance from the National Institute of Health and Care Excellence (NICE) on ITI for patients with haemophilia A who have developed inhibitors to factor VIII.

2 Epidemiology

FVIII deficiency (haemophilia A) is an X-linked recessive disorder occurring in about 1 in every 5,000 male births; there is no ethnic predominance.[9] Severe haemophilia A (factor levels less than 1%) represent approximately 60% of cases, moderate (factor levels of 1 to 5%) represent approximately 15% of cases and mild (factor levels of 6% to 30%) represent approximately 25% of cases. [11]

A systematic review of the epidemiology of inhibitors in patients with haemophilia A reported an overall inhibitor prevalence of 5 to 7%. However the prevalence is much higher at 12 to 13% amongst patients with severe disease.[12] In 2011/12, about 7.5% of patients with severe haemophilia A on the United Kingdom Haemophilia Centre Doctors' Organisation (UKHCDO) register were reported to have inhibitors. The prevalence of new FVIII inhibitors in patients with severe FVIII deficiency ranged from 0% to 39%. About 60% of these inhibitors are high titre (>5 BU) and the remaining are low titre (<5 BU), patients are defined as high and low responders respectively.[12] Most patients develop an inhibitor within a relatively short time period of exposure, with a median of 9–12 exposure days. [12]

Very little is actually known about the natural long term history of inhibitors in absence of ITI, but it is possible that spontaneous inhibitor clearance can occur in about 30 to 60% of patients with haemophilia A over time without treatment with ITI. This information comes from exploratory studies therefore more research is required in this area to establish this. [4]

A number of factors are thought to be predictive of poor response to ITI; failure of a previous ITI, inhibitor titre ≥10 BU at ITI start, peak titre higher than 200 BU, age at ITI start over 7 years old and more than 24 months between inhibitor diagnosis and ITI start.[14]

[c] Bypassing agents are agents that are able to bypass the factor VIII–dependent step in the clotting cascade and promote haemostasis by enhancing thrombin generation.

3 The intervention

The only proven method for eradicating inhibitors is immune tolerance induction (ITI). ITI is the regular infusion of FVIII to induce FVIII antigen-specific tolerance. There are a number of ITI protocols; the most common are the Bonn protocol (high-dose FVIII twice daily), the low-dose Van Creveld regimen (low dose FVIII every other day) and the Malmö protocol (high dose FVIII, intravenous immunoglobulin G (IgG) and cyclophosphamide). There is currently no consensus regarding the specifics of ITI treatment, including the factor product source (plasma-derived versus recombinant), factor dose, timing or the use of immune modulation.[13] However the regimes recommended by UKHCDO working group are very widely used in the UK.[10]

4 Findings

We carried out literature searches on 6 August 2015. We searched Medline, Embase, the Cochrane Library, Trip, DARE and NHS Evidence for systematic reviews, clinical trials, comparative studies and economic evaluations of ITI for patients with haemophilia A with inhibitors to factor VIII. We also searched PubMed for the last three months for any recent e-publications ahead of print publication. The search was limited to English language publications in the last 10 years.

We identified two systematic reviews[8, 9] assessing the effects of ITI for treating inhibitors in people with haemophilia A. We did not find any RCTs or comparative studies published subsequent to the systematic reviews; however, we identified one retrospective study[13] and one prospective observational study[14]. We have included these studies because the systematic review only identified and included one RCT.

We identified four economic evaluations of ITI for patients with haemophilia A who have developed inhibitors to factor VIII [16-19] of which we have reported three. We did not include one study because the authors only reported total costs for the different treatment strategies compared. The authors state that they could not carry out a cost-effectiveness analysis due to lack of evidence and data on the effects of long-term clinical outcomes and quality of life of haemophilia patients as well as long-term direct and indirect costs.

4.1 Evidence of effectiveness

Berntorp et al[8] carried out a systematic review of the treatment of haemophilia A and B and of von Willebrand disease. This review included the evaluation of the efficacy of different treatment regimens to induce immune tolerance. This section of the review included 24 studies, all uncontrolled.

The authors reported that most of the studies showed 70 to 80 percent success[d] (complete or partial) rate but state that the studies were difficult to compare because the products, doses, dose intervals and definitions varied.

[d] Complete success (CS) is defined as having undetectable inhibitor titre [<0.6 Bethesda Units (BU)] at 33 months of ITI, FVIII recovery ≥66% and half-life ≥7 h; partial success (PS) is defined as having a reduction in inhibitor titre to <5 BU per mL with FVIII recovery <66% and/or FVIII half-life <6 h associated with clinical response to FVIII therapy not followed by a treatment-limiting anamnestic rise in inhibitors to >5 BU per mL.

These results should be interpreted with caution given that all of the studies were uncontrolled with limited statistical outcomes data. The bias associated with the studies included means that the findings reported may not be valid and/or generalisable.
Athale et al[9] reviewed evidence on the effect of ITI to remove inhibitors in people with haemophilia A and B (different protocols of this therapy versus each other, or versus only bypassing agents). This Cochrane review included one randomised controlled trial (RCT) [13]; the authors found another RCT which had been stopped so this was not included. They did not find any randomised controlled trial-based comparison of ITI with alternate treatment schemes (i.e. bypassing agents for bleeding only). See Table 1 for a summary of results.

The included RCT[13] randomised 115 children with severe haemophilia A with first attempt at ITI to either low dose (50 IU/kg of factor VIII concentrate three times per week) or a high dose (200 IU/kg of factor VIII daily). The study only included patients who had a high chance of responding to ITI treatment (good risk[e]).The authors did not find any statistically significant difference in the success[f] of ITI between treatment arms. However, the trial was underpowered and did not exclude a material difference in outcome between the treatments. The low-dose arm had significantly more bleeding than the high-dose arm but the confidence interval was very wide.

The authors concluded that, although there were no significant differences in success rate between the two dosing regimens, this may have been due to the imprecision of the estimate. The review was very well conducted with a clear record of how it was carried out. The included RCT was of fairly good quality with a low risk of bias; patients were computer-randomised; while there were some dropouts and withdrawals, they were well balanced across treatment arms. There was no reporting of blinding; however given the intervention it was not feasible to blind participants to their treatment but outcome assessors could have been blinded.

Oldenburg et al[14] reported on the effectiveness of ITI in a retrospective cohort study, which included adults and children. Data from 60 patients with haemophilia A (FVIII< 2%) and inhibitors from 22 centres in Spain, Italy and Germany who underwent primary or rescue[g] ITI (with poor risk factors[h]) with plasma-derived FVIII with von Willebrand factor (pdFVIII/VWF) concentrate, were collected. A total of 41 cases of primary ITI and 19 cases of rescue ITI were evaluated. A success (complete and partial success) rate of 88% was reported in primary ITI and 74% in rescue ITI.

The authors concluded that the results of the study justify the use of rescue (patients who had a lower chance of responding to ITI) as well as primary ITI.

Kreuz et al[15] carried out an open-label, uncontrolled, observational ITI study to evaluate the effectiveness of ITI. The 48 participants (with poor risk factors) in this interim analysis received FVIII concentrate (pdFVIII/VWF) for ITI. ‘Low responders’ at the start of ITI (<5 BU) received 50 to 100 IU/kg FVIII daily or every other day and ‘high responders’ (≥5 BU) received 100 IU/kg FVIII

Partial response required achievement of one of the following three criteria; inhibitor titre [<0.6 Bethesda Units (BU), FVIII recovery ≥80% of the predefined reference value of 1.5% per IU per kg and half-life ≥7 h

[e] Good risk patients refers to patients who have not failed previous ITI, peak titre higher between 5 and 200 BU, age at ITI start under 7 years old and less than 24 months between inhibitor diagnosis and ITI start.

[f] Negative inhibitor titer, FVIII recovery > 66% of expected, and FVIII recovery > 6 h

[g] Rescue patients were defined as those who had previously undergone at least one ITI course using rFVIII or pdFVIII concentrate and failed.

[h] Patients with poor risk factors are those who have one or more of the following risks; failure of a previous ITI, inhibitor titre ≥10 BU at ITI start, peak titre higher than 200 BU, age at ITI start over 7 years old and more than 24 months between inhibitor diagnosis and ITI start.

every 12 h. The authors reported that 34 patients (70.8%) achieved complete success, three (6.3%) partial success and one (2.1%) partial response[i]; ITI failed in 10 patients (20.8%).

The authors concluded that treatment with pdFVIII/VWF concentrate, mainly according to the Bonn protocol, resulted in a high ITI success rate in haemophilia A patients with inhibitors and poor prognosis for ITI success.

The results from these two studies should be interpreted with caution because without control arms, it is difficult to draw any conclusions as the successes reported may not all be as a result of the treatment.

[i] Partial response required achievement of one of the following three criteria; inhibitor titre [<0.6 Bethesda Units (BU), FVIII recovery ≥80% of the predefined reference value of 1.5% per IU per kg and half-life ≥7 h

Table 1: Summary of results

Study	Population	Intervention	Comparator	Outcomes/Results
Athale et al 2014[8] 1 RCT – Hay et al. 2012[13] 70 centres (17 countries)	Paediatric male patients < 7 years old (10.7 to 25.3 months) with severe haemophilia A with factor inhibitory antibodies Peak historical inhibitor titre 5 to 200 BU per ml n=115 Only 'good risk' patients were included	Low dose ITI (50 IU/kg factor VIII 3-times per week)	High dose ITI (200 IU/kg of factor VIII daily)	**Total ITI success[j] (LD vs. HD) – 115 patients** 24/58 – 46.6% vs. 22/57 – 38.6% Risk ratio 1.07 (95% CI 0.68 to 1.68) p=0.909 **All bleeding effects (LD vs. HD) – 115 patients** 50/58 -86.2% vs. 36/57 – 63.1% Risk ratio 1.36 (95% CI 1.09 to 1.71) p=0.0019 **CVAD infections(LD vs. HD) – 99 patients with CVAD** 19/47 – 40.4% vs.22/52 - 42.3% Risk ratio 0.96 (95% CI 0.60 to 1.53) no p value reported
Oldenburg et al 2014[14] Retrospective cohort study 22 centres in Germany, Italy and Spain	Children (49) and adult (11) patients with severe or moderately severe haemophilia A with inhibitors (FVIII<2%) n=60 Included patients with risk factors associated with poor ITI prognosis	Primary ITI n=41 (32 children and 9 adults) Dose range – 40IU/kg FVIII 3 times a week to 300IU/kg every 12 hours	Rescue ITI n=19 (17 children and 2 adults) Dose range – 40IU/kg FVIII 3 times a week to 150IU/kg every 12 hours	**ITI success (CS + PS) – Primary vs. Rescue[k]** 88% vs.74% **Complete success– Primary vs. Rescue** 63.4% vs. 36.8% **Partial success** 24.4% vs. 36.8% **Failure** 12.2% vs. 26.3% No p values reported **No comparative data on bleeding was reported** **CVAD infections - Primary vs. Rescue** 4 vs. 3 (no p values reported)
Kreuz et al 2015[15] 27 centres (13 countries)	Male patients with haemophilia A with inhibitors and risk factors associated with poor ITI prognosis* n=48	'Low responders' at ITI start (<5 BU) received 50 to 100 IU/kg FVIII daily, or every other day; 'high responders' (≥5 BU) received 100 IU /kg FVIII every 12 h.	None	**ITI success** 34 patients (70.8%) achieved *CS;* 3 (6.3%) *PS;* 1 (2.1%) *PR*; ITI failed in 10 patients (20.8%). **Bleeding rates during ITI** BEs reported in 36/48 (75%) of patients. 48% of BEs were moderate and 16% were rated severe. **Safety** ADR was reported in 20/48 (41.7%) of patients. 4 were serious ADRs

[j] Negative inhibitor titre, FVIII recovery > 66% of expected, and FVIII recovery > 6 h
[k] Rescue patients were defined as those who had previously undergone at least one ITI course using rFVIII or pdFVIII concentrate and failed.

* Risk factors of poor response to ITI include failure of a previous ITI, inhibitor titre ≥10 BU at ITI start, peak titre >200 BU, age at ITI start >7 years old and >24 months between inhibitor diagnosis and ITI start.

4.2 Trials in progress

Our search of clinicaltrials.gov (search date 15 September 2015) identified two studies:

NCT02479087: Safety/Efficacy Study of immune tolerance induction, by Factor VIII concentrate containing von Willebrand factor, in severe or moderate haemophilia in patients with inhibitors. The estimated study completion date is January 2020.[20].

NCT01051544: Randomised study of first time immunotolerance induction in severe haemophilia A patients with inhibitor at high risk of failure: comparison with FVIII concentrates with or without Von Willebrand factor - RES.I.S.T. Naive (RESIST NAIVE). The estimated study completion date is June 2020.[14]

4.3 Evidence of cost-effectiveness

Earnshaw et al[16] (2015) carried out a study using a decision-analytic model to compare lifetime costs of treating patients with severe haemophilia A with inhibitors using on-demand or prophylaxis treatment with bypassing agents and ITI (high dose FVIII). Data on response to ITI and reduction in bleeding events for patients on prophylaxis and after eradication of inhibitors when on ITI and relapse of inhibitors were derived from published studies. Costs were obtained from standard US costing sources and are reported in 2014 US dollars.

The authors report that patients treated via ITI or prophylactically with bypassing agents, respectively, incurred approximately 77% and 61% fewer bleeding events over their lifetime compared to patients treated via on-demand therapy. In addition, patients treated via ITI were projected to live 4.3 years longer than patients on prophylaxis and on-demand therapy and have 4.3 and 9.9 more QALYs than patients on prophylaxis and on-demand therapy respectively. As a result, the estimated lifetime costs of treating patients with inhibitors was lower for ITI compared with either on-demand treatment or prophylaxis with bypassing agents. ITI is dominant (i.e. less costly and more effective in terms of reducing bleeding events and increasing QALYs).

Probabilistic sensitivity analysis showed that ITI had a probability of 84% of being lower cost, and was cost-effective (ICER ≤$50 000) compared with prophylaxis under all the conditions modelled. In comparing ITI with on-demand treatment, probabilistic sensitivity analysis showed that ITI was cost-saving under 53% of conditions modelled. With a threshold of $100 000 (£66,600), ITI was cost-effective under 61% of conditions modelled, and with one of $50 000 (£33,300), it was cost effective in 64% of conditions. However, there is a fair amount of uncertainty around these results.

The analysis was fairly well conducted with data sources and assumptions clearly reported. However, the study had a number of limitations. The analysis examined the impact of one ITI dose protocol. In reality, haemophilia treatment centres utilise different ITI protocols. Also the comparison of ITI and prophylaxis approaches with on-demand treatment is based on evidence from uncontrolled studies. The generalisability of these costs and cost-effectiveness estimates to the NHS setting in England is unknown.

Rasekh et al[17] (2011) carried out a cost-utility analysis in Iran of ITI therapy with plasma-derived factor VIII concentrates versus on-demand treatment with recombinant-activated FVIIa (rFVIIa) in haemophilia A patients with high titre inhibitors. This study was based on a previous cost-effectiveness study carried out in the UK. To adapt the previous study, the authors replaced the cost data with Iranian estimates of resource use. Three ITI regimens for inhibitor eradication and

one on-demand strategy were considered: high-dose Bonn protocol, low-dose van Creveld (Dutch) protocol, Malmö protocol and an on-demand regimen with rFVIIa.

The authors reported that all ITI regimens were dominant over on-demand treatment, which was both less effective and more expensive. Among the ITI strategies, low-dose dominated Malmö; the incremental cost per QALY gained with the Bonn over Malmö regimens was $249,400 (£164,600) and the incremental cost per QALY gained with the Bonn regimen over low-dose was $842,300 (£556,000). The authors concluded that a low-dose ITI protocol was the most cost-effective option versus both other ITI regimens and on-demand treatment with rFVIIa.

The selection of comparators in this analysis was appropriate as the available treatment strategies for this patient population in the authors' setting were considered. Dosages and administration times were reported clearly. The study relied on a previous cost-effectiveness model but the authors did not report the methodological characteristics of the model or the design of the studies from which clinical parameters were taken. No Iranian estimates were found and no sensitivity analysis was conducted, so it was not possible to judge the validity of the clinical side of the study.

The economic analysis included only the costs of the treatments. The authors pointed out that the cost of clotting factor concentrates accounted for 98% of total costs. However, it is unclear if the inclusion of other direct medical and indirect costs would have substantially altered the results of the analysis. The cost of clotting factors was varied in the sensitivity analyses but the results were not reported. The authors acknowledged some limitations of their analysis related mainly to the need for assumptions and lack of Iranian data. The study results are unlikely to be relevant to the England NHS setting.

Knight et al[18] (2003) carried out a systematic review of the cost-effectiveness of treatment options in patients with haemophilia A with inhibitors. However, because of the paucity of published evidence, they undertook an economic modelling exercise to calculate the cost-effectiveness of different strategies in the treatment of high-responding haemophilia A patients with inhibitors. They used a decision analysis approach to model the expected lifetime clinical outcomes and costs of the more common regimens used in the UK in treating severe haemophiliacs with inhibitors. Three ITI (Bonn, Malmö and low-dose) and three on-demand regimens were compared.

The results of the economic modelling indicate that the Malmö ITI protocol is the preferred treatment strategy for haemophilia A patients who have high-responding inhibitors, generating more quality adjusted life-years (QALYs) and less cost than either an on-demand regimen or the Bonn or low-dose ITI protocols. The Bonn ITI protocol had highest cost but generated the largest gain in QALYs (33.1) because it is the most successful ITI protocol. The low-dose ITI protocol costs less than the Bonn ITI protocol but has fewer QALYs gained (29.1). The Malmö ITI protocol had the lowest average lifetime cost but the fewest QALYs gained (28.1) above the OD protocol (25.1).

The Malmö ITI protocol dominates the on-demand strategy as it has both a lower average lifetime cost and higher QALYs gained (cost/QALY not stated). The cost/QALY gained for the low-dose ITI protocol compared with the on-demand protocol was around £56,000. The cost/QALY gained for the Bonn ITI protocol compared with the on-demand protocol was around £148,000.

Sensitivity analysis did not have any major effects on the results of the cost-effectiveness analysis with the Malmö ITI protocol remaining dominant most of the time. However, the sensitivity

analysis of the treatment duration for the low-dose ITI protocol showed that, if the duration of treatment was reduced while still maintaining the same success rate, the low-dose ITI protocol would become the preferred choice of treatment compared with the on demand regimens. The Malmö ITI protocol is not that widely used within the UK.

The analysis was well conducted with all assumptions, sources of data and cost clearly reported. One of the limitations of this study is that the ITI strategies were not compared to prophylactic treatment with bypassing agents. Also because the analysis was carried out in 2003, the management strategies compared and the relative costs are likely to be out of date.

4.4 Safety

The RCT conducted by Hay et al. reported that central venous access device (CVAD) infection was the most common complication observed in children with severe haemophilia and inhibitors. A total of 124 CVAD infections were reported in 41 of 99 (41%) subjects with an overall infection rate of 0.94 per 1000 CVAD-days. A similar number of infections were observed in the two treatment arms. Infections occurred more frequently in the presence of external catheters than with fully implanted catheters ($P = 0.026$). ITI outcome was unaffected by CVAD infections.

Other adverse events reported include haemarthrosis, febrile convulsion, gingivitis and allergic reaction to FVIII.

4.5 Summary of section 4

Clinical effectiveness

Evidence from one RCT (115 patients with good risk) showed no statistically significant difference in the success of ITI between low-dose and high-dose ITI treatment arms in patients with haemophilia A with inhibitors however; the confidence intervals were too wide to infer no effect. The low-dose arm had significantly more bleeding than the high-dose arm for this reason the study was stopped early but again the confidence interval was very wide.

Uncontrolled studies report that ITI has a 70 to 80 percent success rate in haemophilic patients with inhibitors. Because spontaneous clearance of inhibitors might have occurred in some of the participants without ITI, these studies form an unreliable basis for estimating the effectiveness of the treatment.

Cost-effectiveness

We have reported three economic evaluations (from Iran, the USA and the UK) of ITI for patients with haemophilia A who have developed inhibitors to factor VIII. All the three studies suggest that ITI is cost-effective compared to prophylaxis and on-demand treatment with bypassing agents. However the analyses are based mostly on low quality clinical evidence.

Safety

Central venous access device (CVAD) infection was the most common complication observed in children with severe haemophilia and inhibitors in the frame of the I-ITI study. Other adverse events reported include haemarthrosis, febrile convulsion, gingivitis and allergic reaction to FVIII.

5 Discussion and conclusions

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.

We did not identify any studies comparing ITI with alternative treatment schemes.

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

Evidence from one the only UK conducted economic analysis suggests that the Malmo protocol is the most cost-effective ITI regimen. The sensitivity analysis carried out suggests that low dose ITI is likely to be the most cost-effective ITI 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.

6 References

1. Bolton-Maggs PHB, Pasi KJ. Haemophilias A and B. Lancet 2003; 361: 1801–9.
2. Srivastava A, Brewer AK, Mauser- Bunschoten EP et al. Treatment Guidelines Working Group on Behalf of the World Federation of Hemophilia. Guidelines for the management of hemophilia. Haemophilia 2013; 19: e1–47.
3. Kempton CL, White GC II. How we treat a hemophilia A patient with a factor VIII inhibitor. Blood 2009; 113: 11–17.
4. Tagariello G, Iorio A, Matino D et al. High rate of spontaneous inhibitor clearance during the long term observation study of a single cohort of 524 haemophilia A patients not undergoing immunotolerance. J Hematol Oncol 2013; 6. (Published on-line). Witmer C, Young G. Factor VIII inhibitors in hemophilia A: rationale and latest evidence. *Therapeutic Advances in Hematology* 2013; 4(1):59-72.
5. Brown T, Lee W, Joshi A et al. Health-related quality of life and productivity impact in haemophilia patients with inhibitors. Haemophilia 2009; 15: 911–17.
6. DiMinno MND, DiMinno G, DiCapua M et al. Cost of care of haemophilia with inhibitors. Haemophilia 2010; 16: e190–201.
7. Earnshaw SR, Graham CN, McDade CL et al. Factor VIII alloantibody inhibitors: cost analysis of immune tolerance induction vs. prophylaxis and on-demand with bypass treatment. Haemophilia 2015; 21: 310–319.
8. Berntorp E, Astermark J, Baghaei F et al. Treatment of hemophilia A and B and von Willebrand disease. Stockholm: The Swedish Council on Health Technology Assessment (SBU). Yellow. 2011
9. Athale AH, Marcucci M, Iorio A. Immune tolerance induction for treating inhibitors in people with congenital haemophilia A or B. *Cochrane Database of Systematic Reviews* 2014, Issue 4. Art. No.: CD010561.
10. Collins PW, Chalmers E, Hart DP et al. 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. British Journal of Haematology, 2013, 160, 153–170
11. https://www.hemophilia.org/Bleeding-Disorders/Types-of-Bleeding-Disorders/Hemophilia-A
12. Wight J and Paisley S. The epidemiology of inhibitors in haemophilia A: a systematic review. Haemophilia 2003; 9: 418–435.
13. Hay CR, DiMichele DM. International Immune Tolerance Study. The principal results of the International Immune Tolerance Study: a randomized dose comparison. Blood 2012; 119: 1335–44.
14. Oldenburg J, Jiménez-Yuste V, Peiró-Jordán R et al. Primary and rescue immune tolerance induction in children and adults: a multicentre international study with a VWF-containing plasma-derived FVIII concentrate. Haemophilia 2014; 20: 83–91.
15. Kreuz W, Escuriola Ettingshausen C, Vdovin V. et al on behalf of the ObsITI study group and the ObsITI committee. First prospective report on immune tolerance in poor risk haemophilia A inhibitor patients with a single factor VIII/von Willebrand factor concentrate in an observational immune tolerance induction study. Haemophilia 2015; 1-9.
16. Earnshaw SR, Graham CN, McDade CL et al. Factor VIII alloantibody inhibitors: cost analysis of immune tolerance induction vs. prophylaxis and on-demand with bypass treatment. Haemophilia2015; 21: 310–319
17. Rasekh HR, Imani A, Karimi M et al. Cost-utility analysis of immune tolerance induction therapy versus on-demand treatment with recombinant factor VII for hemophilia A with high titer inhibitors in Iran. ClinicoEconomics and Outcomes Research 2011; 3(1): 207-212
18. Knight C, Paisley S, Wight J et al. Economic modelling of different treatment strategies for hemophilia A with high-responding inhibitors. Hemophilia 2003; 9: 521-540.
19. Berger K, Schopohl D, Eheberg D et al. Treatment of children with severe haemophilia A and inhibitors: a health economic evaluation for Germany. Klinische Padiatrie. 2013 May; 225(3):152-8.
20. https://clinicaltrials.gov/ct2/show/NCT01051544

7 Search Strategy

Population, Intervention, Comparator and Outcomes (PICO)

P- Patients/ population Which patients or populations of patients are we interested in? How can they be best described? Are there subgroups that need to be considered?	*Adults and children with haemophilia A with 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* *(Around 25-30% of children with severe haemophilia A form antibodies against administered factor VIII after commencing treatment. In 2011/12 there were 46 new patients with severe haemophilia A registered on the UKHCDO database. Of these, 35 were under the age of 19 years. The incidence of haemophilia A patients under the age of 19 years in the UK who develop inhibitors is likely to be around 9-12 per year.)*
I - Intervention Which intervention, treatment or approach should be used?	*Immune tolerance therapy administered in accordance with* ***UKHCDO protocol for first line immune tolerance induction for children with severe haemophilia A:*** *UKHCDO Inhibitor and Paediatric Working Parties -21st January 2013* N.b. has application for adults too.
C - Comparison What is/ are the main alternative/s to compare with the intervention being considered?	The two principle products available for this are recombinant factor VIIa (rFVIIa, Novoseven) and factor VIII bypassing agent (FEIBA). Any intervention
O - Outcomes What is really important for the patient? Which outcomes should be considered? Examples include intermediate or short-term outcomes; mortality; morbidity and quality of life; treatment complications; adverse effects; rates of relapse; late morbidity and re-admission; return to work, physical and social functioning, resource use.	• Survival • Bleeding frequency and severity • Inhibitor titre • Use/cost of clotting factor products • Admissions and hospital attendances • Adverse events/safety • Joint damage and other complications • Loss of education/working days • Restriction of daily activities • Quality of life. .

Search date: 06 August 2015
Databases searched: Medline, Embase, Cochrane, TRIP, DARE and NICE Evidence Search - limited to studies published in English and last 10 years. PubMed - the last three months for any recent e-publications ahead of print publication. Conference papers, letters and case reports excluded.

Embase search:

Searches

1. hemophilia A/
2. (hemophilia a or haemophilia a or (sever* adj2 (hemophilia or haemophilia))).ti,ab.
3. (hemophilia* or haemophilia*).ti.
4. 1 or 2 or 3
5. immunological tolerance/
6. (immun* tolerance adj3 (therap* or treat* or induction*)).ti,ab.
7. immunotolerance.ti,ab.
8. immun* tolerance.ti.
9. 5 or 6 or 7 or 8
10. 4 and 9
11. limit 10 to (english language and yr="2005 -Current")
12. limit 11 to "reviews (maximizes specificity)"
13. limit 11 to "therapy (best balance of sensitivity and specificity)"
14. limit 13 to "economics (maximizes sensitivity)"
15. limit 10 to (english language and yr="2013 -Current")