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Immune tolerance induction for treating inhibitors in people with congenital haemophilia A or B (Review)

Athale AH, Marcucci M, Iorio A

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[Intervention Review]

Immune tolerance induction for treating inhibitors in people with congenital haemophilia A or B

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ABSTRACT

Background

The occurrence of factor inhibitory antibodies, or inhibitors, is a significant complication in the care of individuals with congenital haemophilia A or B. Currently, immune tolerance induction is the only known intervention to successfully eradicate inhibitors. However, ideal dosing regimens, and the comparative safety and efficacy of different immune tolerance induction regimens have not yet been established.

Objectives

The objective of this review was to assess the effects of immune tolerance induction (different protocols of this therapy versus each other, or versus only bypassing agents) for treating inhibitors in people with congenital haemophilia A or B.

Search methods

We searched the Cochrane Cystic Fibrosis and Genetic Disorders Group's Coagulopathies Trials Register, compiled from electronic database searches and handsearching of journals and conference abstract books. We also searched: MEDLINE (from 1946 to 15 July 2013); Embase (from 1980 to 15 July 2013) via the OVID platform; CINAHL (from conception to 15 July 2013); and ClinicalTrials.gov (most recent search: 15 July 2013). We also searched the reference lists of relevant articles and reviews.

Selection criteria

Randomised controlled trials comparing either different immune tolerance induction regimens or immune tolerance induction versus only bypassing therapy for the eradication of factor inhibitory antibodies in patients with congenital haemophilia A or B.

Data collection and analysis

Two review authors independently completed data collection, extraction and assessment of the risk of bias of trials.

Main results

One methodologically sound randomised controlled trial met the inclusion criteria and was included in the review. One further randomised controlled trial has been recently stopped, but it has not yet been reported.

The included multinational trial randomised 115 paediatric participants with severe haemophilia A and high-responding inhibitors, for whom this was the first attempt at immune tolerance induction, to receive either a low dose (50 IU/kg of factor VIII concentrate three times per week) or a high dose (200 IU/kg of factor VIII daily). Although, there was no statistically significant difference in the success of immune tolerance induction between treatment arms, the confidence intervals were too wide to infer no effect: 24 out of 58 participants (46.6%) in the low-dose group and 22 out of 57 (38.6%) in the high-dose group experiencing full tolerance, risk ratio 1.07 (95% CI 0.68 to 1.68) (moderate quality evidence). The rate of infection was not statistically different between groups, but again confidence intervals were too wide. Of those patients who had a central venous catheter device, 19 out of 47 participants (40.4%) in the low-dose arm had 69 infections, and 22 out of 52 participants (42.3%) in the high-dose arm had 55 infections, risk ratio 0.96 (95% CI 0.60 to 1.53) (moderate quality evidence). However, participants in the low-dose immune tolerance induction group experienced significantly more bleeding episodes (50 out of 58 participants (86.2%) experienced one or more bleeding events) than those in the high-dose group (36 out of 57 participants (63.1%) experienced one or more bleeding events), risk ratio 1.36 (95% CI 1.09 to 1.71) (low quality evidence). One factor VIII reaction, one incidence of trauma and 13 incidences of needing to insert or remove the catheter were reported as trial-related serious adverse events; however, the treatment group where these events occurred was not specified. No incidence of nephrotic syndrome was reported.

Authors' conclusions

We did not find any randomised controlled trial-based comparison of immune tolerance induction with alternate treatment schemes (i.e. bypassing agents for bleeding only). In a single randomised trial, there were no significant differences in the immune tolerance induction success rate between different dosing regimens, which may have been due to imprecision of the estimate. There is low-quality evidence to suggest that high-dose immune tolerance induction may induce tolerance more quickly which is associated with fewer bleeding complications. The choice of immune tolerance induction regimen should be considered individually for each case, until further research provides additional evidence.

PLAIN LANGUAGE SUMMARY

Immune tolerance induction to destroy inhibitors in people with haemophilia A or B

Review question

We reviewed evidence about the effect of immune tolerance induction to remove inhibitors in people with haemophilia A and B.

Background

Haemophilia A and B are inherited bleeding disorders, where affected people are missing a clotting factor in their blood, which is needed for normal blood clotting. Without this factor, people with haemophilia cannot make proper clots, and they may bleed for a much longer time than normal after an injury, or may experience sudden and unexpected bleeding inside the body and into joints. These bleeding incidents can cause permanent damage to the affected area and can be life threatening. The current treatment for haemophilia is replacement therapy, where the missing clotting factor is injected into the blood. Sometimes, when the missing clotting factor is introduced, the person's immune system will think it is a foreign body, and try to eliminate it with molecules called inhibitors. When a person with haemophilia develops an inhibitor, the injected clotting factor is destroyed before it can stop the bleeding. This is a very serious problem that affects almost one in three people with haemophilia A and approximately one in 30 people with haemophilia B. Immune tolerance induction is a treatment to make the immune system get used to the clotting factor, so that it no longer rejects the factor. This treatment, which involves giving large doses of factor concentrate, is currently used at different doses. We are unsure of how the dosing options work and how safe they are. To discover this, we searched the evidence until July 2013.

Trial characteristics

We found one randomised trial that compared high- and low-dose immune tolerance induction, which included 115 males with haemophilia A and inhibitors.

Key results and conclusions

The single included trial was too small to be certain that both doses of immune tolerance induction were equally successful at removing inhibitors. However, the high-dose treatment destroyed all inhibitors faster and with less bleeding events than the low-dose treatment. Since there was only one available trial, further trials are needed to establish the best immune tolerance induction regimen with respect to starting time, dosing intensity and frequency.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Low-dose ITI compared with high-dose ITI for inhibitor eradication				
Patient or population: persons with severe haemophilia A and factor inhibitory antibodies Settings: one included trial is a multi-national, multi-centre trial Intervention: low-dose ITI (50 IU/kg of FVIII 3-times per week) Comparison: high-dose ITI (200 IU/kg of FVIII daily)				
Outcomes	Relative effect (95% CI) ⁴	No of Participants (studies)	Quality of the evidence (GRADE) ¹	Comments
Total ITI Success	RR 1.07 (0.68 to 1.68)	115 participants (1study)	⊕⊕⊕○ moderate ²	
All bleeding events	RR 1.36 (1.09 to 1.71)	115 participants (1study)	⊕⊕○○ low ^{2,3}	
CVAD infections	RR 0.96 (0.60 to 1.53)	99 participants (1study)	⊕⊕⊕○ moderate ²	Of 115 participants, only 99 were reported to have a CVAD, and CVAD infections were the only type of infections reported
Severe allergic reaction				Treatment group of single allergic event was not available, hence could not assess this outcome
Nephrotic syndrome				No data available

GRADE Working Group grades of evidence

High quality: further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: we are very uncertain about the estimate.

¹Since there was only one included trial, we could not assess inconsistency, and we did not use this criterion to rate down.

²Downgraded for imprecision: one included study did not give us sufficient confidence about the precision of our result, and we cannot fully exclude a difference among the two regimens.

³Downgraded for risk of bias: given that the outcomes were self-reported, we thought the lack of blinding of participants may have introduced bias in outcome assessment.

⁴Information about rate of spontaneous inhibitor tolerance (i.e. a control group) is not available in the literature, hence we cannot calculate and include risks for the control group. However, in a cohort of 79 high responding inhibitor patients, who did not undergo ITIT, 23 (29%) cleared the inhibitor over a median of 6 years ([Tagariello 2013](#)).

CI: confidence Interval

CVAD: central venous access device

FVIII: factor VIII

GRADE: Grading of Recommendations Assessment, Development and Evaluation

BACKGROUND

Description of the condition

Haemophilia A and B are congenital X-linked inherited blood disorders. While haemophilia A (estimated incidence rate of 1 per 5000 live births) is more common than haemophilia B (estimated incidence rate of 1 per 30,000 live births), both conditions are caused by the partial or complete absence of coagulation factor VIII or IX, respectively (Mannucci 2001). Diminished levels of the coagulation factor disrupts the blood clotting mechanism in affected individuals to different degrees depending on the level of factor present: mild haemophilia (clotting factors levels greater than 5 IU/dL); moderate haemophilia (clotting factor levels between 1 and 5 IU/dL); and severe haemophilia (clotting factor levels below 1 IU/dL) (Coppola 2010).

Individuals with haemophilia are at increased risk for adverse outcomes, such as excessive and uncontrollable bleeding when experiencing external trauma or undergoing surgical procedures. These conditions can negatively affect the quality of life of an affected individual. Individuals with mild or moderate haemophilia rarely experience spontaneous bleeding episodes, and often only bleed after experiencing major trauma or undergoing invasive procedures. Individuals with severe haemophilia are at highest risk for severe and frequent spontaneous bleeding incidences, and often experience recurrent or chronic bleeding into joints and muscles, which can evolve into joint arthropathy.

Individuals receiving factor VIII or IX replacement therapy can develop antibodies against factor VIII or IX, called inhibitors, which interfere with factor coagulation activity by neutralising the effect of exogenous factor concentrate. Inhibitor development is a major challenge to the care of individuals with haemophilia, as their development can preclude safe and effective therapy of factor concentrate infusion. Disease type and severity influences inhibitor development. The odds of developing inhibitory antibodies are higher soon after the beginning of treatment and in people with severe haemophilia A (estimated incidence: 30%) compared to people with haemophilia B (estimated incidence: 3%) (Coppola 2010; DiMichele 2007). Individuals with more severe haemophilia are also more likely to develop inhibitory antibodies. There are two main goals of treatment for individuals who have haemophilia and develop inhibitors: the first is to efficiently manage bleeding episodes, which is usually done with bypassing agents such as recombinant activated factor VII, the second goal is to eradicate inhibitor presence with interventions such as immune tolerance induction (ITI) (Iorio 2010).

Description of the intervention

Currently, strategies addressing inhibitor reduction and eradication are diverse and heterogenous. For individuals with low-responding inhibitors, administration of increased dosages of factor VIII or IX can be used to manage the presence of inhibitors during bleeding episodes. In the case of high-responding inhibitors, to date, ITI is the preferential treatment to eradicate inhibitors in people with haemophilia (Di Michele 2011). While the exact mechanism through which ITI can induce tolerance remains unclear, the general concept is that large doses of factor concentrate may decrease immune response through decreased production of factor inhibitory antibodies. Proposed molecular mechanisms include clonal deletion, anergy and ignorance of specific cellular targets (Astermark 2011). Treatment with ITI involves the frequent administration of factor VIII or IX concentrate to patients with inhibitors, with the long-term goal of eradicating inhibitor presence. It should be noted, that in people with haemophilia B who have developed inhibitors, factor IX can only be used for low-responding inhibitors or ITI, when the individual does not experience an allergic reaction to factor IX or products containing factor IX (DiMichele 2007). Central venous access devices (CVADs), which are commonly used to administer treatment in patients with haemophilia and inhibitors, are associated with many complications including CVAD-associated infections and thromboses (Komvilaisak 2006). Aside from allergic reactions, another complication associated with ITI is development of nephrotic syndrome, which is particular to individuals with haemophilia B and inhibitors (DiMichele 2007).

Other interventions to manage inhibitor levels include the use of bypassing agents (such as recombinant activated factor VIIa or aPCC), which can be used to manage inhibitors in the event of bleeding episodes. Also, the use of immunosuppressive drugs, such as prednisone, oral cyclophosphamide or rituximab (an anti-CD20 monoclonal antibody), work to suppress immune system function and have been shown to aid eradication of inhibitors in people with congenital haemophilia A and B (Carcao 2006). Further, immunoadsorption strategies to remove immunoglobulin factor antibodies, via highly specific extracorporeal perfusion of blood and plasma, have been used to reduce high inhibitor levels to allow for more effective ITI (Freedman 2003; Freedman 2004). However, the use of and the regimen given for these interventions are heterogeneous.

Literature reporting on the administration and regimen used for ITI is very varied. Much of the current knowledge has been gleaned from people with haemophilia A, with limited data regarding ITI use in those with haemophilia B. Prior studies investigating the use

of ITI have employed numerous regimens with regards to dosage, timing and type of concentrate, among other variables. Universal protocols for ITI in people with haemophilia A and B do not yet exist.

How the intervention might work

The development of inhibitors in people with haemophilia poses many challenges to care. Patients who develop inhibitory antibodies for factor VIII or IX have been shown to experience increased adverse outcomes. According to Tagliaferri, having an inhibitor was associated with higher mortality rates (Tagliaferri 2010). Furthermore, individuals developing inhibitors require a more extensive, and often more complicated, treatment regimen to manage their disease than individuals of comparable disease severity, who do not develop inhibitors (Gringeri 2003). Inhibitor development in the haemophilia population has been related to increased orthopedic complications that results in a lower quality of life (Gringeri 2003; Scalone 2006). From an economic standpoint, inhibitor development drastically increases the cost of care, thereby increasing the economic burden (Di Minno 2010). The use of ITI, with its potential to eradicate inhibitory antibodies in individuals with haemophilia A and B, might be an avenue to re-establish normalisation of treatment in individuals who have developed inhibitory antibodies.

Why it is important to do this review

In patients with haemophilia, the development of inhibitors after the commencement of therapy instigates many challenges for both the healthcare provider and the patient. Treatment with ITI presents one method of countering the effects of inhibitors in this group. However, existing studies provide no unequivocal results on the ideal time of ITI initiation, the optimal regimen, and actual effectiveness. The proposed review aims to summarise the evidence with regards to ITI in the haemophilia population. We wish to compare ITI between different factor-based regimens and to other interventions used with patients with haemophilia who develop inhibitors, to evaluate its effect on inhibitor eradication. Results of this review may be used to inform future research, to aid clinicians in making informed clinical decisions, and perhaps may be the first step in promoting the creation of universal ITI protocols.

OBJECTIVES

To determine the efficacy and adverse effects of ITI in people with congenital haemophilia A and B and inhibitors.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) and controlled clinical trials (CCTs), both published and unpublished, were eligible for inclusion in any publication form (i.e. abstract, letter, article, etc).

Types of participants

Individuals (without any age or sex restrictions) who have been diagnosed with congenital haemophilia A or B, and who have factor VIII or IX inhibitors. We excluded individuals with acquired haemophilia.

Types of interventions

Immune tolerance induction, which is the administration of any form (plasma-derived or recombinant factor of any preparation marketed under any brand name) of factor VIII or IX with the intent of eradicating the inhibitor. We considered trials including all variations regarding dosage, timing, duration and mode of delivery for ITI.

We considered the following comparisons:

1. ITI versus other factor concentrate based regimens (i.e. different ITI protocols, which may be supplemented with bypassing agents to control bleeding events);
2. ITI (any regimen) versus use of only bypassing agents.

Types of outcome measures

Primary outcomes

1. Efficacy: inhibitor eradication, defined as
 - i) unmeasurable inhibitor
 - ii) normal factor VIII or IX recovery
 - iii) normal factor VIII or IX half-life
2. Safety: incidence of adverse events (such as musculoskeletal bleeding events, all bleeding events, administration site infections, severe allergic reactions (SAE), and nephrotic syndrome)

Secondary outcomes

1. Joint function (measured using a validated scale, e.g. the Haemophilia Joint Health Score (HJHS), the Denver Score, or the Orthopaedic Joint Score (OJS))

2. Quality of life (measured using a validated scale, e.g. the haemophilia-specific quality of life questionnaire (Hemo-QoL), the Canadian Hemophilia Outcomes-Kids Life Assessment Tool (CHO-KLAT), the 36-item short-form SF-36, or the EuroQoL Group's five-dimension questionnaire (EQ-5D))

3. Cost and resource utilisation (any costs relating to the treatment including, but not limited to, cost of coagulation factors, and costs associated with hospital visits or hospitalisations due to bleeding events).

The stated secondary outcome of cost and resource utilisation will be measured through cost-effectiveness data, through reported incremental cost effectiveness ratios (ICERs) using quality adjusted life years (QALYs).

Search methods for identification of studies

Electronic searches

We searched the Cochrane Cystic Fibrosis and Genetic Disorders Group's Coagulopathies Trials Register for relevant studies using the terms: (factor VIII* OR factor IX) AND haemophilia*.

The Coagulopathies Register is compiled from electronic searches of the Cochrane Central Register of Controlled Trials (CENTRAL) (updated for each new issue of *The Cochrane Library*), quarterly searches of MEDLINE and prospective hand-searching of one specialised journal, *Haemophilia*. Unpublished work is identified by searching the abstract books of five major conferences: the European Haematology Association conference; the American Society of Hematology conference; the British Society for Haematology Annual Scientific Meeting; the International Society of Haemostasis and Thrombosis Congresses; and the International Congresses of World Federation of Haemophilia. For full details of all searching activities for the register, please see the relevant section of the [Cochrane Cystic Fibrosis and Genetic Disorders Group Module](#).

In addition, we performed searches in the MEDLINE and Embase databases (using the Ovid platform). We also searched the CINAHL database for relevant reports. We searched each database from the earliest possible date (for MEDLINE: January 1946, for Embase: January 1974; and for CINAHL: January 1950) to July 15 2013. The full search strategies are available in the appendices of the review ([Appendix 1](#); [Appendix 2](#); [Appendix 3](#)). There were no language restrictions placed on these searches.

Searching other resources

We reviewed the bibliographic reference lists of all retrieved studies for additional eligible trials. We also searched trial registries, such as ClinicalTrials.gov (www.clinicaltrials.gov) and the International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/en/) to identify ongoing trials.

Data collection and analysis

Selection of studies

Two authors (AA, MM) independently reviewed the abstracts from the search results to identify articles that might be relevant to the review. Two authors retrieved the full texts (unless only published in abstract form) for those articles considered to be potentially relevant to the review. The same two authors assessed the full text manuscripts to select the included trial. The authors discussed conflicting cases until they reached a consensus.

Data extraction and management

Two authors (AA, MM) independently extracted data using pre-designed data forms. The same two authors resolved any differences in data extraction through discussion. The authors extracted data on the following topics from the included trial:

- inclusion criteria of trial;
- location and time frame of trial;
- participant number and demographics;
- trial methods;
- trial design;
- type, characteristics and duration of the intervention and control (if applicable) groups;
- outcome measures and description;
- information regarding limitations or bias (or both).

Assessment of risk of bias in included studies

The authors assessed the risk of bias in the included trial using the Cochrane Collaboration's tool for assessing risk of bias' as outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)). For the included trial, we assessed and classified the following seven criteria as having either a 'high risk', 'low risk' or 'unclear risk' of bias.

1. Sequence generation
2. Allocation concealment
3. Blinding of participants and personnel
4. Blinding of outcome assessment
5. Incomplete outcome data
6. Selective outcome reporting
7. Other issues

Measures of treatment effect

The one included trial reported ITI success as a dichotomous outcome (i.e. yes or no that the individual had successful tolerance). We used a risk ratio (RR) and the corresponding 95% confidence intervals (CI) to measure treatment effect.

In future updates, where there may be heterogeneity in outcome reporting, we plan to use the following measures of treatment effect

- Outcomes represented as a rate: we will use a rate ratio, with the corresponding CIs.
- Continuous outcomes: we will use a standardized mean difference (SMD), with the corresponding CIs.
- Time-to-event data: we will use a hazard ratio, with the corresponding CIs.
- Economic data: we will use point estimates, with the corresponding measure of variance (such as standard deviation (SD)). We also plan to report ranges of cost data, if it is the more appropriate treatment measure. If our search provides multiple trials that report cost data, we will critically evaluate the data, taking into account the measurement and reporting methods and the context of the trial. If data are deemed to be similar enough and are equivalent across studies, we will pool data using methodology described in the *Cochrane Handbook for Systematic Reviews* (Shemilt 2011). Given that the pooling of economic data can be very controversial, if we report data in this way, we will present a critical analysis of the data in the results to ensure transparency and reproducibility. If we do not pool economic data, we will include a narrative summary of these data in the review.

Unit of analysis issues

Given that haemophilia, related treatments and potential for complications can be variable between individuals, we expected that the unit of analysis for most of the trials to be the individual. For this review, we did not expect to find any cluster-randomised trials as feasibility would have been a concern for cluster trials. Furthermore, ITI for inhibitor eradication is not an appropriate treatment to study in a cross-over trial. In the future, if we encounter trials with multiple intervention groups, we plan to combine treatment groups to create a single pair-wise comparison that is most relevant to our outcome.

Dealing with missing data

Where data were missing from the included trial, we applied an intention-to-treat analysis, as was also employed by the trial authors. We also noted levels of missing data, and the reasons why they were missing. We did not attempt to contact trial authors for missing data.

Assessment of heterogeneity

Since only one trial was eligible for inclusion in this review, we did not need to assess heterogeneity. In future updates of this review, if we include more trials, we will assess heterogeneity as outlined in our original protocol, as follows.

If we include multiple trials in future revisions of this review, we will initially identify statistical heterogeneity by using the Chi² test, with the null hypothesis being that there is no significant heterogeneity across trial results. We will conclude that the results

of the trials are not heterogeneous if we cannot reject the null hypothesis (i.e. if there is no statistically significant difference between the different trials). As suggested by the *Cochrane Handbook for Systematic Reviews of Interventions*, to have a more conservative test we will use a significance level of $P = 0.1$ rather than $P = 0.05$. This will help us have further confidence that a non-significant result indicates a lack of homogeneity.

We will conduct a meta-analysis if there are multiple trials with consistent treatment effects. We will use the I^2 method to provide evidence for heterogeneity in our meta-analysis. Our interpretation thresholds, as suggested in the *Cochrane Handbook for Systematic Reviews of Interventions*, will be as follows (Deeks 2011):

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity;
- 75% to 100%: considerable heterogeneity.

Final interpretation will depend on number and characteristics of the retrieved studies.

Assessment of reporting biases

Since only one trial was included, it was not appropriate to construct a funnel plot to assess reporting bias. Instead, we compared the data reported in the trial report to the trial protocol to detect any differences that may be attributable to reporting bias.

For future updates of the review, if more trials are included in the review, to detect reporting bias, we plan to construct a funnel plot and assess it for symmetry. If any asymmetry is detected, then we plan to investigate the cause to see if it is attributable to reporting bias. If there are greater than 10 trials included in the funnel plot, then we will use the test proposed by Egger to test for asymmetry (Egger 1997). Further, in an attempt to identify selective reporting, we will compare information as reported in trial protocols with the actual methods and outcomes reported in the published papers in an attempt to identify any differences.

Data synthesis

We had originally planned to statistically combine data in a meta-analysis to acquire one estimate of treatment effect. However, with only one eligible trial, data synthesis was not possible. If more than one trial is included in future updates of this review, and it is appropriate to combine trials, we will synthesize data as outlined in our original protocol, as follows.

We plan to undertake a fixed-effect model analysis and to switch to random-effects model use if we identify substantial or considerable heterogeneity in our meta-analysis. We will evaluate heterogeneity as described above.

Subgroup analysis and investigation of heterogeneity

In order to investigate any heterogeneity in future updates, if we include a sufficient number of trials (n = 10), we plan to undertake the following four subgroup analyses for each of our primary outcomes:

1. patients for whom this is the first ITI attempt versus if ITI has been previously attempted;
2. ITI in individuals who developed an inhibitor as previously-untreated patients versus those as previously-treated patients;
3. ITI in adults versus children;
4. ITI in patients with high titer inhibitors (more than 5 Bethesda units (BU)) versus low titer inhibitors (less than 5 BU). However, these groups were not addressed in the one eligible trial.

Sensitivity analysis

For future updates of this review, if there are a sufficient number of comparable trials (10 or more), we will perform sensitivity analyses to exclude trials with clearly inadequate allocation of concealment, randomisation, or blinding (high risk of bias). If possible, we will also explore the impact of including trials with high levels of missing data in the overall assessment of treatment effect. A high level of missing data is defined as any level of missing data that is sufficient to reverse the treatment effect.

Summary of findings table

Please refer to the summary of findings table ([Summary of findings for the main comparison](#)).

We included all assessable outcomes, from the one included trial in the summary of findings table. We used the GRADE approach to assess the quality of evidence. However, since there was only one included trial we were unable to assess inconsistency for all included outcomes. We hope that with the addition of more trials we will be able to assess this GRADE category in future updates.

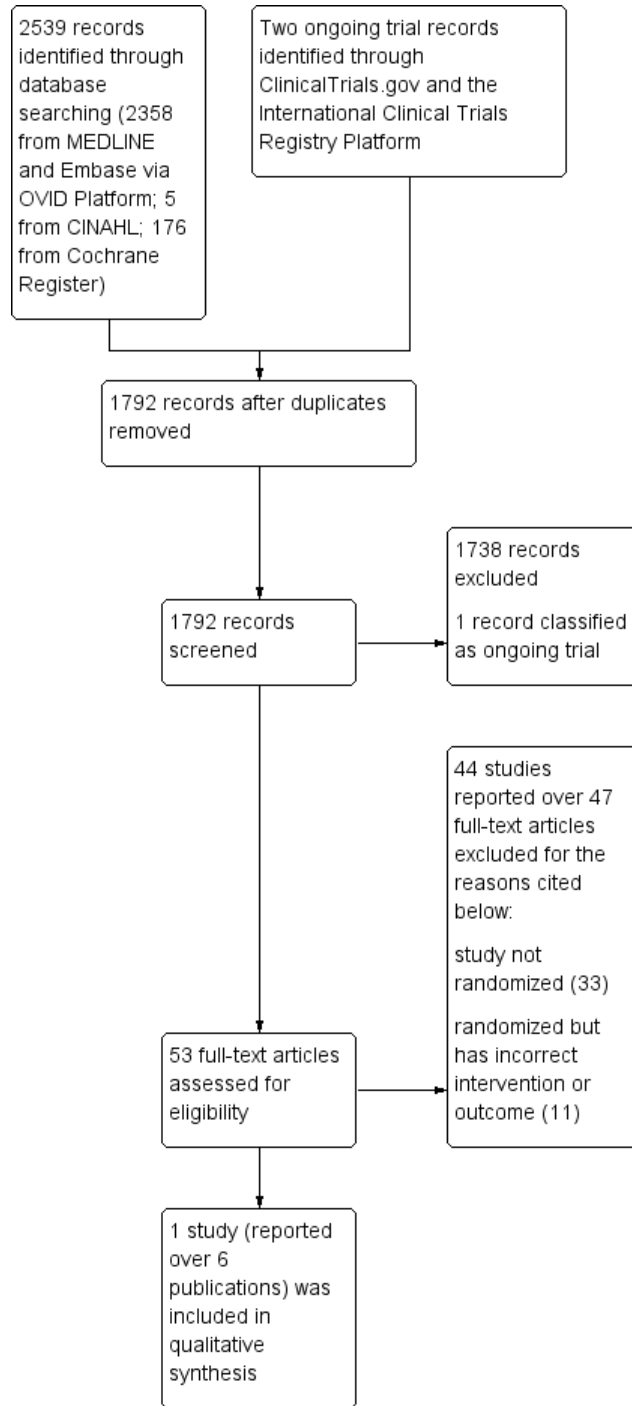
RESULTS

Description of studies

Results of the search

For the detailed trial selection flow chart, please refer to the figures section ([Figure 1](#)).

Figure 1. Study flow diagram.



The searches identified 1792 potential articles (after duplicates were removed). Two review authors independently conducted initial screening at the title level. At this point, 1738 records were excluded as they did not meet the inclusion criteria. One article was classified as ongoing ([NCT01051544](#)). The full text of each of the remaining 53 articles was retrieved and assessed for eligibility and of these, one trial (six references) was included in the review ([Hay 2012](#)) and 47 articles reporting 44 unique trials were excluded.

Included studies

One trial was eligible for inclusion, the 'International Immune Tolerance Induction (I-ITI) Trial', which included 115 patients ([Hay 2012](#)).

The Hay trial was a multicentre, prospective RCT, which was conducted in 70 centres spanning 17 countries. The trial aimed to compare the efficacy and safety of high-dose versus low-dose ITI, under the hypothesis that ITI outcome is independent of dosing regimen. The trial was stopped early because of futility and safety concerns, as there were significantly more bleeding events in the low-dose arm compared to the high-dose arm.

In all, 134 male patients less than seven years of age, with severe haemophilia A, who had a high-responding inhibitory antibody to factor VIII were enrolled in the trial. All patients were identified as 'good-risk' meaning an expected favourable response to ITI, as predicted by their peak historical inhibitor titre was between 5 and 200 BU/mL, and the starting inhibitor titre was 10 BU/mL or less prior to randomisation or decreased to this level in less than 12 months. Of enrolled participants, 10 were removed from the trial prior to randomisation, and eight participants were awaiting randomisation at the time of trial termination. A further participant was withdrawn from the trial after randomisation but before starting ITI, and hence was excluded from the analysis.

Of the remaining 115 participants included in the analysis, 58 participants were randomised to receive low-dose ITI (50 IU/kg of factor VIII three times per week), and 57 participants were randomised to receive high-dose ITI (200 IU/kg of factor VIII daily). The primary endpoint was ITI outcome (either successful tolerance, partial response, trial failure, or relapse) ([Hay 2012](#)).

Excluded studies

A total of 47 articles reporting 44 unique studies were excluded, of these, 35 articles reported on non-randomised studies and 12 were reported as having a randomised trial design but were excluded because they had the incorrect intervention or incorrect outcomes, or both.

Ongoing studies

One study, the RESIST NAIVE, was characterised as 'ongoing' ([NCT01051544](#)).

The RESIST NAIVE study is a prospective, RCT, which has been recently stopped for difficulty in recruiting participants. It planned to investigate the safety and efficacy of ITI on patients with severe haemophilia A who have not previously undergone ITI, but have a risk factor for ITI failure, such as having a peak inhibitor titer more than 200 BU, having an inhibitor titer more than 10 BU at ITI start, being older than seven years of age or having the time between inhibitor occurrence and ITI more than two years ([NCT01051544](#)).

Risk of bias in included studies

Please refer to the figures section of the review ([Figure 2](#); [Figure 3](#)).

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

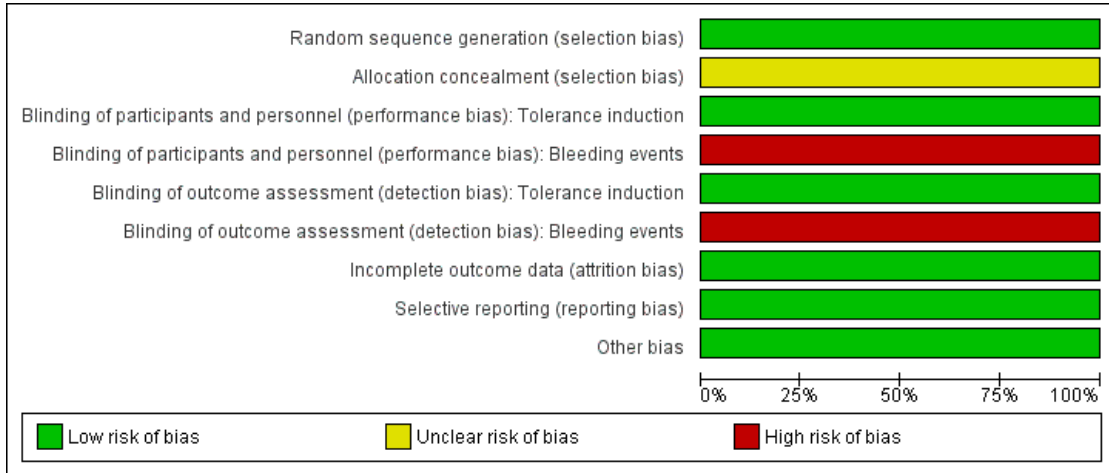











Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

Hay 2012									
	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias): Tolerance induction	Blinding of participants and personnel (performance bias): Bleeding events	Blinding of outcome assessment (detection bias): Tolerance induction	Blinding of outcome assessment (detection bias): Bleeding events	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias

We assessed the risk of bias for the included trial was according to the pre-defined criteria given in the methods section ([Methods](#)). Overall, we considered the included trial to be at a low risk for bias.

Allocation

The included trial was judged to have a low risk of bias for random sequence generation as it was reported that patients were computer randomised using minimization for product type (either plasma derived or recombinant) and starting inhibitor titre (either above or below 5 BU/mL). However, as the trial reports did not indicate the method of allocation concealment, this category was judged as having an unclear risk of bias.

Blinding

There was no reporting of blinding, at any level. Given the intervention it was not not feasible to blind participants to their treatment allocation. However, it perhaps would have been possible to blind outcome assessors. This lack of blinding was judged to have variable effects on the bias introduced for the various outcomes. For the primary outcome of tolerance induction, which is an objective and laboratory-confirmed endpoint, we did not think that the lack of blinding would have much effect on the interpretation of results, and hence judged this category to be at low risk of bias. However, for secondary outcomes that were self-reported (i.e. frequency of bleeding events), the lack of blinding may have impacted outcome assessment. Hence, we judged this category to be at high risk of bias for the secondary outcomes. In light of this, results for secondary outcomes should be interpreted with caution.

Incomplete outcome data

While there were some dropouts and withdrawals reported in the included trial, they were balanced across treatment arms and reasons for leaving the trial were well-documented. Further, analysis was conducted on an intention-to-treat basis. For these reasons we judged this category to be at low risk of bias.

Selective reporting

We judged this category to be at low risk of bias because the reported outcomes match those listed in the protocol, and are comprehensively reported.

Other potential sources of bias

We did not identify any other potential sources of bias.

Effects of interventions

See: [Summary of findings for the main comparison](#)

No meta-analysis could be completed as there was only one eligible trial. As more trials are available for inclusion, future updates of this review may include statistical pooling of data.

Given the participants included in this trial, three out of our four pre-specified subgroups (first ITI attempt versus previous ITI event, ITI for PTPs versus ITI for PUPs, and ITI for adults versus children) were not addressed in this trial. Data for our fourth subgroup (ITI in patients with high titer inhibitors (more than five BU) versus low titer inhibitors (less than five BU)) were not reported.

Data from the one eligible and included trial (n = 115) are reported below ([Hay 2012](#)).

Primary Outcomes

1. Efficacy: total ITI success

For the one included trial, the primary outcome was ITI tolerance, which was analogous to our primary outcome of inhibitor eradication ([Hay 2012](#)). Participants who reached successful ITI tolerance all had a negative inhibitor titer, factor VIII recovery was more than 66% of expected, and factor VIII recovery more than six hours. There was no significant difference in participants achieving tolerance between the two treatment groups; overall 24 participants on low-dose ITI and 22 participants on high-dose ITI achieved successful tolerance, RR 1.07 (95% CI 0.68 to 1.68) (115 participants) ([Analysis 1.1](#)).

2. Safety

a. Musculoskeletal bleeding

Separate data for different types of bleeding events were not reported in the included trial, hence we could not statistically pool the data. However, in their report, the trial authors stated that there was no statistically significant difference between treatment arms in terms of musculoskeletal bleeding incidents.

b. All bleeding events

In the included trial, there were significantly more bleeding events in the low-dose arm than in the high-dose arm over the course of ITI treatment, RR 1.36 (95% CI 1.09 to 1.71) (115 participants) ([Analysis 1.2](#)).

c. Infection

The eligible trial reported the number of CVAD infections (Hay 2012). Of the 58 low-dose participants, 47 had a CVAD, and of the 57 high-dose participants, 52 had a CVAD. Of patients who had a CVAD, 19 in the low-dose arm had 69 infections, and 22 participants in the high-dose arm had 55 infections. There were no significant differences in incidence of CVAD infections, RR 0.96 (95% CI 0.60, 1.53) (99 participants) (Analysis 1.2). Ten non-catheter-related infections were reported, however, they were deemed to be not trial related, and their distribution over trial arms was not reported.

d. Severe allergic reactions (SAE)

One factor VIII reaction was reported as a trial-related SAE. However, the treatment group where this reaction occurred was not reported.

e. Nephrotic syndrome

No incidence of nephrotic syndrome was reported.

f. Other adverse events

Other trial-related serious adverse events included trauma (n = 1) or need to insert or remove catheter (n = 13). However, the distribution over trial arms was not reported. We did not contact the trial authors to establish which arm contributed to the adverse events.

Secondary outcomes

1. Joint function

This outcome was not assessed in the included trial (Hay 2012).

2. Quality of life

This outcome was not assessed in the included trial (Hay 2012).

3. Cost and resource utilisation

Cost-effectiveness was a reported outcome in the trial, however, data were not available at the time of this review.

DISCUSSION

Summary of main results

There was no statistically significant difference in successful tolerance to factor VIII in people with severe haemophilia A and a factor inhibitory antibody, who received high-dose compared to low-dose ITI with factor VIII concentrates. However, those receiving low-dose ITI experienced significantly more bleeding events than those receiving high-dose ITI.

Overall completeness and applicability of evidence

This review consists of one RCT comparing two ITI dosing regimens (Hay 2012). However, the results and conclusions that can be drawn from the review have limited external validity, as they are only applicable to good-risk, paediatric participants with severe haemophilia A, who had not previously tried ITI for inhibitor eradication. We were unable to address any of our secondary outcomes, as there were no data available for these analyses. Further, because of the specific participant types, we were unable to undertake our pre-planned subgroup analyses for our primary efficacy and safety outcomes. Future RCTs investigating the safety and efficacy of ITI in different patient populations (i.e. participants with different severity of haemophilia, of different ages, with different dosing regimens, etc) will help to improve the external validity of this review in future updates. Unfortunately, it is not likely that other trials will be undertaken in the near future, and the RESIST NAIVE trial, designed to fill some of this gap in information, has been recently discontinued (NCT01051544).

The included trial is the first and only prospective, RCT conducted to compare ITI efficacy and safety in patients with severe haemophilia A and inhibitors, and provided valuable evidence to inform ITI treatment (Hay 2012). Despite being stopped early, this trial shows that RCTs can feasibly be conducted in rare disease populations. The trial was a multicentre, international trial, which perhaps suggests that ITI practice is, or can be, standardised internationally. In addition to the advantages of the prospective, randomised design, the strengths of the included trial include the use of pre-defined study endpoints and international data collection. Further, this trial provided valuable prospective evidence about the pharmacokinetics of factor VIII during ITI and the year following successful tolerance; it also identified peak inhibitor titer in ITI as a significant predictor of ITI outcome in the multivariate-regression analysis.

The results of the Hay trial suggest that both high-dose and low-dose ITI can be used in inducing immune tolerance in haemophilia A patients with factor inhibitory antibodies. Despite the trial being stopped early, the results suggest that there is no significant difference between ITI success rate in both groups. Given this, future cost-effectiveness and quality of life analyses may influence the choice of dosing regimen in different populations. Accordingly, recent guidelines indicate that the use of ITI and choice of dosing regimen should be considered on a case-by-case basis (Benson 2012). The 50 IU/kg every other day can be seen as low-

dose ITI or high-dose prophylaxis. For patients and clinicians in low-income settings, it is valuable to know that continuing on a prophylaxis-like regimen will achieve the same rate of inhibitor clearance as the high-dose regimen. It remains for future research to understand the value of continuing inhibitor patients on low-dose prophylaxis regimens such as those used in China, Egypt, Algeria and Thailand (median dose being 10 to 15 IU/kg two to three times per week).

Since the population of the included trial was limited to patients with severe haemophilia A, the results have limited generalizability to patients with haemophilia B. To date, the treatment of haemophilia B complicated with an inhibitor is guided by anecdotal case reports, case studies or observational studies, as there are no existing guidelines or more methodologically rigorous study in this area. Given the low prevalence of haemophilia B and the even lower incidence of inhibitor development, conducting adequately-powered trials to prospectively evaluate the efficacy and safety of ITI in patients with haemophilia B and inhibitors would be challenging. However, in comparison to treatment of inhibitors in people with haemophilia A, treatment of inhibitors in patients with haemophilia B has a history of increased morbidity due to severe allergic reactions following administration of factor IX and development of nephrotic syndrome (Batorova 2013). Given this, treatment of inhibitors in patients with haemophilia B (i.e. by using ITI) while perhaps more challenging, is definitely separate from the treatment of inhibitors in haemophilia A and thus warrants separate evidence-based guidance. However, due to the extreme rarity of the condition, it is unlikely that strong evidence will be available for this area in the foreseeable future.

Upon recommendation by an independent data and safety monitoring board, the included trial was terminated early for safety concerns, as there were significantly more bleeding events in the low-dose group than in the high-dose group, and fertility concerns, mainly due to slow recruitment and unlikelihood of reaching the necessary sample size. At the time the trial was terminated, only 135 patients had been recruited and throughout the course of the trial 966 bleeding events had been reported (684 in the low-dose group and 282 in the high-dose group). The original power calculation indicated that 75 patients would be needed per arm to have an adequately-powered trial, which would allow for two interim analyses to be conducted after recruitment of 50 and 100 participants. No formal stopping rules were indicated. As a consequence, the trial was underpowered and was limited in its ability to assess the primary outcome. To date, investigators have not reported long-term treatment effects and long-term adverse events.

Quality of the evidence

The current body of randomised evidence to inform the use of ITI for inhibitor eradication in haemophilia patients is comprised of one trial that includes 115 patients. By outcome, the body of evidence is moderate for the primary outcome of the review (ITI

success), and low for assessable secondary outcomes (bleeding frequency and infection). Please refer to summary of findings table for the rationale of the evidence assessment (Summary of findings for the main comparison). The included trial is novel in the field of haemophilia and has many methodological strengths. Since there is only one eligible RCT, the results of this review are directly applicable only to a limited group. We believe that further research is likely to have an impact on the effect estimates presented in this review. Currently ITI is the most widely adopted method to eradicate inhibitory antibodies. Hence, given the limited amount of randomised evidence, clinicians and policy makers might also consider high-quality, non-randomised evidence when making decisions.

Potential biases in the review process

To our knowledge, our review process is free from bias. We took the following steps to limit bias: our search strategy was reviewed multiple times to ensure that all relevant trials would be captured; we searched different sources of data (including different databases, and clinical trial registries); we pre-specified all outcomes and subgroups; we completed all screening in duplicate with a third-party arbitrator; and we extracted data in duplicate. Future updates of this review will use similar safeguards to limit bias in the review process.

Agreements and disagreements with other studies or reviews

With the exception of the international ITI trial by Hay (Hay 2012), the evidence to inform current clinical practice decisions for ITI treatment come from registry data and observational studies, which are largely retrospective cohort studies or case series (Di Michele 2011; Franchini 2011). Success with ITI and factors that affect ITI outcome have been retrospectively and prospectively observed in registries, such as the International Immune Tolerance Registry (IITR) (Mariani 1999), the North American Immune Tolerance Registry (NAITR) (DiMichele 2009), the German Immune Tolerance Registry (GITR) (Lenk 2000) and the Spanish Registry (Haya 2001). A further registry, the Prognostic Factors in Immune Tolerance (PROFIT), is currently still collecting data (Coppola 2009). Each of these registries has collected data about ITI dosing regimens and successes. Authors of the included trial indicated that the lower overall ITI success rate in their trial in comparison to reporter registry rates is likely attributed to the use of a standardised definition of ITI success, which has not been universally used, and the use of an intention-to-treat analysis that included all patients - both compliant and non-compliant (Hay 2012).

There is some congruence between registry data and the current trial regarding factors that predict ITI outcome. The NAITR,

IITR, the Spanish Registry and PROFIT all identified pre-ITI titer level to be a significant predictor of ITI outcome (Coppola 2009; DiMichele 2009; Haya 2001; Mariani 1999). The NAITR, GITR, IITR and the Spanish Registry all identified historical peak titer level to be a predictor of ITI outcome (DiMichele 2009; Haya 2001; Lenk 2000; Mariani 1999). The NAITR and PROFIT registry found that peak inhibitor titre while on ITI was a significant predictor of ITI success (Coppola 2009; DiMichele 2009). In comparison, the results of the Hay trial showed that peak historical titer and peak inhibitor titer, while on ITI, were significant predictors of ITI outcome in the univariate analysis and peak inhibitor titer on ITI was the only significant predictor of ITI outcome in a multivariate regression (Hay 2012).

With respect to dosing options, a previously completed meta-analysis of the IITR and NAITR registries showed that the ITI success rate was similar in good-risk patients receiving either high- or low-dose ITI (Kroner 1999). This finding is in concordance with the results of the included trial (Hay 2012). However, since the trial was stopped early, it did not have sufficient statistical power to establish therapeutic efficacy. In addition to ITI regimens using only factor concentrates for inhibitor eradication, some ITI protocols use immune modulation methods to help improve ITI success. Such strategies have had similar success rates to ITI protocols without immune modulation (Berntorp 2000). Further research will need to be conducted to establish the efficacy of ITI protocols with immune modulation, in comparison to those without immune modulation.

In addition to the ITI registries, two additional non-randomised studies are ongoing that aim to assess the efficacy and safety of ITI for inhibitor eradication in people with haemophilia (Kreuz 2014; NCT01051076). The RESIST EXP trial is a prospective observational study, which is currently ongoing and recruiting participants; their target date to complete enrolment is June 2020. RESIST EXP is investigating the efficacy of ITI in participants who have previously failed ITI with von Willebrand factor (VWF)-free factor VIII concentrates (NCT01051076). The Observational Immune Tolerance Induction (ObsITI) Research Program is an ongoing international, open-label, uncontrolled, non-interventional, multicentre observational research program that aims to document ITI success in patients treated with the Bonn ITI protocol. As a secondary aim, the program is investigating different factors that may influence ITI outcome. As of February 2013, 256 patients from 27 countries have been enrolled (Kreuz 2014).

Two prior reviews were published to assess ITI in people with haemophilia. A systematic review by Wight considered the use of ITI in patients with haemophilia A and inhibitors (Wight 2003). However, this review was conducted prior to the publication of the Hay trial and conclusions were based on observational evidence. Due to the heterogeneity of the results, statistical pooling of data was not possible (Wight 2003). A more recent review by Franchini reviewed the use of ITI in patients with severe haemophilia A, but was also completed prior to the publication of the results of

the International Immune Tolerance Induction Study (Franchini 2011). While neither previous review included the Hay trial, both narratively reviewed available observational data but were unable to statistically combine these data.

The choice of ITI regimen (i.e. high- or low-dose) may also be influenced by cost since there is an eight times higher factor consumption in the high-dose arm compared to the low-dose arm. The increased cost of treatment of high-dose ITI, however, might be balanced by the cost of treatment for bleeds in patients with inhibitors. A recent cost minimisation analysis suggests that adjusting factor dose according to bleeding risk status might lower the cost associated with ITI (Odeyemi 2009). However, further analyses are necessary to determine the most cost-effective ITI regimen.

AUTHORS' CONCLUSIONS

Implications for practice

Even in the absence of RCT-based evidence of tolerogenic effect, ITI is the most widely adopted method to eradicate factor inhibitory antibodies. Compared to low-dose ITI, high-dose ITI may be associated with fewer bleeding complications, but without significant difference in the proportion of those eventually achieving tolerance. However, this lack of statistical significance may be due to imprecision as the single included trial was underpowered. Until further evidence is available, the use of ITI and the regimen to adopt should be considered individually on a case-by-case basis.

Implications for research

Further research is needed in areas such as the use of immune modulating agents as adjunct to ITI, use of ITI in different patient populations, and of different ITI dosing regimens.

Prospective data relating to quality of life, joint health and cost-effectiveness of ITI will help improve knowledge about different treatment dimensions of haemophilia patients with inhibitors. In addition, the use of standardised outcome definitions, as used in the included trial, will help the future statistical pooling of data.

Haemophilia is a rare disease, within which incidence of inhibitors is even more rare. This can make it quite difficult to design and conduct a controlled trial with adequate power to establish statistical superiority, equivalence or non-inferiority. While the Hay trial is proof that a randomised trial design can be conducted in a rare disease population such as haemophilia patients with inhibitors, there are some scenarios (i.e. ITI in patients with haemophilia B) where a randomised design would be unsuitable, inefficient, or unfeasible (Hay 2012).

The termination of the I-ITI study for futility illustrates the difficulties in conducting RCTs to assess differences in inhibitor erad-

ication strategies. However, the results of this systematic review point to the possible role of different regimens in minimizing bleeding episodes. This leaves the field open to future comparative studies. Sequential or adaptive designs, risk or allocation designs or bayesian-decision analysis trials might help fill the information gaps.

As to the absence of RCT-based evidence of the tolerogenic effect of ITI, while it is highly unlikely and possibly unethical to randomise patients to be treated or not in the wealthy world, every

effort should be made, in the less wealthy countries to obtain as much information as possible on the natural history of inhibitors in patients undergoing alternative treatments adopted when ITI is not feasible (Caram 2011; Tagariello 2013).

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Hay 2012

Methods	Parallel RCT: computer randomisation using minimisation for product type and starting inhibitor titre level
Participants	115 participants with severe haemophilia A, and a FVIII inhibitory antibody underwent randomisation (58 on LD ITI and 57 on HD ITI). Median age at randomisation (months): 15.6 (LD) versus 14.4 (HD); median inhibitor titre at randomisation (BU/mL): 5.9 (LD) vs 5.1 (HD); median total time on ITI (months) 16.4 (LD) vs 14.2 (HD)
Interventions	Participants were randomised to either LD ITI of 50 IU/kg of FVIII 3-times weekly or HD ITI of 200 IU/kg of FVIII daily. Product choice and use of central venous access devices was left to discretion of the clinician at each participating centre. Switching FVIII brand or source was not permitted
Outcomes	Outcomes reported were: 1) ITI success rates; 2) bleeding events; 3) CVAD infections; 4) allergic reactions
Notes	After tolerance was achieved, participants were given prophylaxis treatment with 30 IU/kg of FVIII 3-times a week Central confirmation of 'critical inhibitor measurements'. Pre-defined, universal outcome measures. Trial was stopped early for futility and safety concerns.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Reported that patients were computer randomised using minimization for product type (either plasma-derived or recombinant) and starting inhibitor titre (either above or below 5 BU/mL). However, the allocation ratio was not stated
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment was not reported.
Blinding of participants and personnel (performance bias) Tolerance induction	Low risk	While not reported, given the nature of the intervention, it was not possible to blind participants to the treatment allocation. However, the primary endpoints of the trial were objective, laboratory confirmed endpoints. Hence, the lack of blinding may have less of an impact on such objective outcomes, in comparison to more subjective

		tive outcomes
Blinding of participants and personnel (performance bias) Bleeding events	High risk	While not reported, given the nature of the intervention, it was not possible to blind participants to the treatment allocation. For patient-reported outcomes like bleeding, the lack of blinding may have impacted outcome reporting
Blinding of outcome assessment (detection bias) Tolerance induction	Low risk	Blinding status of outcome assessors was not reported. However, we do not anticipate that lack of blinding would have much impact in the objectively measured primary outcome. Further, investigators remained blinded for the interim analyses by the DSMB
Blinding of outcome assessment (detection bias) Bleeding events	High risk	Blinding status of outcome assessors was not reported. For patient-reported outcomes such as bleeding, the lack of blinding may have impacted outcome assessment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Originally 116 participants were randomised, but 1 was withdrawn by investigator prior to starting ITI, and was not included in the analysis. Of the 115 randomised participants included in the analysis, 21 were withdrawn before reaching a defined trial endpoint (8 were withdrawn by physicians or parents, 12 were withdrawn for poor compliance of major protocol violations, and 1 participant was lost to follow up after reaching tolerance). However, withdrawals were reported to be balanced across treatment arms (12 HD vs 9 LD). Further, analysis was conducted on an intention-to-treat basis
Selective reporting (reporting bias)	Low risk	There is no evidence to suggest that there is selective reporting present in the trial report, and the data presented seem very comprehensive. All outcomes listed in the protocol (found on clinicaltrials.gov ; identifier: NCT00212472) were addressed in the study report. All outcomes, except cost-effectiveness comparison between treatment arms, are reported in the primary report. This report states that the “comparative pharmaco-economic analysis of the 2

		treatment arms is ongoing and will be reported separately.” At the time of this review, information about cost-effectiveness was not yet available
Other bias	Low risk	No other sources of bias are expected.

BU: Bethesda units
 DSAB: Data Safety and Monitoring Board
 FVIII: factor VIII
 HD: high dose
 ITI: immune tolerance induction
 LD: low dose
 mL: millilitre
 RCT: randomised controlled trial

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Astermark 2007	No ITI comparison arm, and outcome was different.
Baker 2010	Non-randomised: case series.
Battle 1999	Non-randomised: case series.
Berger 2009	Non-randomised: case series.
Berntorp 2005	No ITI comparison arm.
Carneiro 2002	Non-randomised: case series.
Ewenstein 2000	Incorrect intervention.
Ewing 1988	Non-randomised: case series.
Gouw 2013	Incorrect intervention: regular dosing of FVIII with outcome of inhibitor development
Gruppo 1992	Non-randomised: case series.
Kasuda 2004	Non-randomised: case series.
Klukowska 2005	Non-randomised: case series.
Klukowska 2010	Non-randomised: case series.

(Continued)

Klukowska 2012	Non-randomised: case series.
Klukowska 2013	Non-randomised: retrospective analysis.
Konkle 2007	Incorrect intervention (rFVIIa) and no ITI arm.
Kucharski 1996	Non-randomised: case series.
Kurth 2008	Non-randomised: retrospective analysis.
Lusher 1980	Incorrect intervention (aPCC).
Lusher 1983	Incorrect intervention (aPCC versus non-activated PCC).
Lusher 1998	Incorrect intervention: trial considered FVIIa for haemorrhage
Manco-Johnson 2002	Non-randomised study: case series.
Mariani 2001	Non-randomised study: editorial article.
Meeks 2013	Non-randomised study: retrospective analysis.
Nilsson 1988	Non-randomised study: case series.
Nilsson 1990	Non-randomised study: case series.
Orsini 2005	Non-randomised study: retrospective analysis.
Palomo 2010	Non-randomised study: case report.
Platokouki 2009	Non-randomised study: case series.
Prentice 1984	Incorrect outcome: bleeding events.
Puetz 2011	Non-randomised study: case series.
Rocino 1999	Non-randomised study: case series.
Rocino 2004	Non-randomised study: case series.
Rothschild 1998	Non-randomised study: case series.
Santagostino 2012	Non-randomised study: retrospective analysis.
Scaraggi 2004	Non-randomised study: case series.
Seremetis 1994	Incorrect intervention: FVIIa for bleeding events..

(Continued)

Shapiro 1998	Incorrect intervention: FVIIa for bleeding during surgery.
Stiefel 2010	Non-randomised study: case report.
Svirin 2008	Non-randomised study: case series.
Unavar 2000	Non-randomised study: case series.
Valentino 2008	Non-randomised study: case series.
Van Velzen 2012	Non-randomised study: retrospective analysis.
Zozulya 2008	Non-randomised study: prospective observational study.

aPCC: activated prothrombin complex concentrates

FVIIa: factor VIIa

FVIII: factor VIII

ITI: immune tolerance induction

PCC: prothrombin complex concentrates

rFVIIa: recombinant activated factor VIIa

Characteristics of ongoing studies [ordered by study ID]

NCT01051544

Trial name or title	Trial of first time ITI in severe haemophilia A patients with inhibitor at high risk of failure: comparison with FVIII concentrates with or without VWF - RES.I.S.T. Naive (RESIST NAIVE)
Methods	Listed as a randomised, open-label, parallel group trial.
Participants	Estimated enrolment of 148 male participants of any age who have severe haemophilia A and high-responding inhibitors. Eligible participants must also have at least 1 of the following risk factors for ITI failure: (1) peak inhibitor titer > 200 BU; (2) titer at ITI start > 10 BU; (3) age > 7 years; or (4) time between inhibitor occurrence and ITI > 2 years
Interventions	FVIII concentrates with and without von Willebrand concentrates
Outcomes	Primary: successful ITI, which is defined as: "the abolition of the inhibitor to < 0.6 BU within 33 months of ITI with a factor VIII recovery \geq 66% and half-life \geq 6 hrs, and measured after a 72-hour washout period." Secondary: (1) absence of relapse; (2) time to achieve success; (3) compliance to treatment; and (4) cost of care
Starting date	June 2009.

NCT01051544 (Continued)

Contact information	Principal investigator: Nadia P Ewing, City of Hope National Medical Center, Department of Pediatrics, 1500 E. Duarte Rd. Duarte, CA 91010
Notes	

BU: Bethesda units

FVIII: factor VIII

HD: high dose

ITI: immune tolerance induction

LD: low dose

VWF: von Willebrand factor

DATA AND ANALYSES

Comparison 1. Low-dose ITI versus high-dose ITI

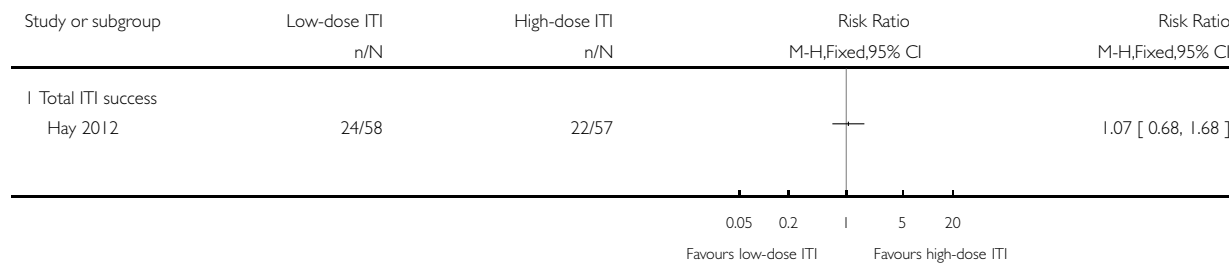
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Efficacy	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 Total ITI success	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Safety	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.1 All bleeding events	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 CVAD infections	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 1.1. Comparison 1 Low-dose ITI versus high-dose ITI, Outcome 1 Efficacy.

Review: Immune tolerance induction for treating inhibitors in people with congenital haemophilia A or B

Comparison: 1 Low-dose ITI versus high-dose ITI

Outcome: 1 Efficacy

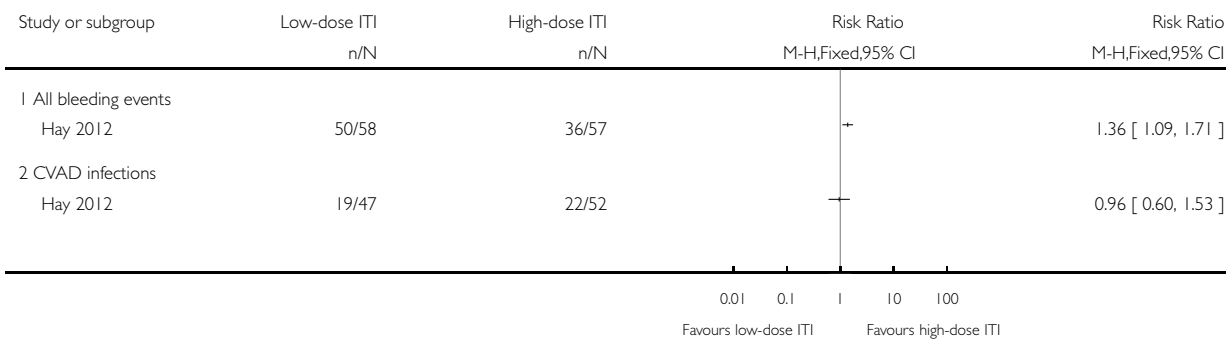


Analysis 1.2. Comparison 1 Low-dose ITI versus high-dose ITI, Outcome 2 Safety.

Review: Immune tolerance induction for treating inhibitors in people with congenital haemophilia A or B

Comparison: 1 Low-dose ITI versus high-dose ITI

Outcome: 2 Safety



APPENDICES

Appendix I. Search strategy for MEDLINE and Embase via OVID platform (last search July 15 2013)

Search terms

- 1 Hemophilia A/
- 2 Hemophilia B/
- 3 Hemophilia A.mp.
- 4 Hemophilia B.mp.
- 5 Haemophilia A.mp.
- 6 Haemophilia B.mp.
- 7 Hemophil:.mp.
- 8 Haemophil:.mp.
- 9 Factor VIII/
- 10 Factor VIII.mp.
- 11 Factor 8.mp.
- 12 Factor XI/
- 13 Factor XI.mp.
- 14 Factor 9.mp.
- 15 Clotting factor.mp.
- 16 Recombinate.mp.
- 17 Kogenate.mp.

(Continued)

18 Helixate.mp.
19 Advate.mp.
20 Xyntha.mp.
21 Refacto.mp.
22 Benefix.mp.
23 Humate P.mp.
24 Fandhi.mp.
25 Alphanate.mp.
26 Alphanine.mp.
27 Wilate.mp.
28 Immunate.mp.
29 Immunine.mp.
30 Hemophil.mp.
31 Nonacog.mp.
32 Koate.mp.
33 Cryobulin.mp.
34 haemophilus influenzae/
35 haemophilus [influenzae.mp.](#)
36 hemophilus [influenzae.mp.](#)
37 34 or 35 or 36
38 1 or 2
39 3 or 4 or 5 or 6
40 7 or 8
41 40 not 37
42 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30
or 31 or 32 or 33
43 39 or 41 or 42
44 inhibi:.mp.
45 43 and 44
46 38 and 45
47 Immune Tolerance/
48 immune [tolerance.mp.](#)
49 immune tolerance [induction.mp.](#)
50 ITI.mp. (1076)
51 [immunotolerance.mp.](#)
52 Bonn [protocol.mp.](#)
53 malmo [protocol.mp.](#)
54 47 or 48 or 49 or 50 or 51 or 52 or 53
55 46 and 54
56 limit 55 to humans

Appendix 2. Search strategy for CINAHL (July 15 2013)

search terms
1. Hemophilia OR FIX OR FVII 2. Inhibitor OR antibody 3. 1 AND 2

Appendix 3. Search terms for trials registry (July 15 2013)

Search terms
1. Hemophilia 2. Inhibitors 3. 1 AND 2

WHAT'S NEW

Last assessed as up-to-date: 16 April 2014.

Date	Event	Description
13 April 2015	Amended	Contact details updated.

CONTRIBUTIONS OF AUTHORS

Task	Who will undertake the task?
<i>Protocol stage:</i> draft the protocol	All authors
<i>Review stage:</i> select which trials to include	AA, MM (AI as arbiter)
<i>Review stage:</i> extract data from trials	AA, MM
<i>Review stage:</i> enter data into RevMan	AA
<i>Review stage:</i> carry out the analysis	All authors

(Continued)

<i>Review stage:</i> interpret the analysis	All authors
<i>Review stage:</i> draft the final review	All authors
<i>Update stage:</i> update the review	AA

DECLARATIONS OF INTEREST

None known.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

For this version of this review, there were no differences between the protocol and the review.

INDEX TERMS

Medical Subject Headings (MeSH)

*Immune Tolerance; Early Termination of Clinical Trials; Factor VIII [*administration & dosage; immunology]; Hemophilia A [immunology; *therapy]; Hemophilia B [immunology; *therapy]; Immunosuppression [*methods]

MeSH check words

Humans; Male