Immune tolerance induction in hemophilia patients with inhibitors: costly can be cheaper
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Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
Two strategies for the management of inhibitory antibodies to factor VIII (FVIII) in patients with severe haemophilia A were examined. The strategies were the treatment of bleeding episodes with large quantities of haemostatic agents, or immune tolerance induction (ITI) followed by standard FVIII replacement. Haemostatic agents include porcine FVIII, prothrombin complex concentrates (active or not) and recombinant factor VIIa. ITI involves the daily infusion of large doses of FVIII over many months to years, as well as the use of immunosuppressive agents and other procedures. The dosage depends on the patient weight and severity of bleeding.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised a hypothetical cohort of patients with severe haemophilia A and a high responding inhibitor of 25 Bethesda units (BU).

Setting
The setting was secondary care and a hospital. The economic study was carried out in the USA.

Dates to which data relate
The effectiveness and resource use data were derived from studies published between 1988 and 1999. The price year was not reported.

Source of effectiveness data
The effectiveness evidence was derived from a synthesis of completed studies.

Modelling
A Markov model was constructed to examine the costs and survival associated with the two alternative strategies under evaluation in a hypothetical 5-year-old boy with severe haemophilia A and a high responding inhibitor of 25 BU. The initial weight of the patient was 20 kg and it increased linearly over 15 years to a final weight of 70 kg. Patients could move across seven possible health states. Three health states were defined by short-term morbidity only (minor, moderate and major), three were defined by short-term morbidity superimposed on irreversible arthropathy, and the remaining one was death. Minor short-term morbidity was defined as minor bleeding episodes treated at home with a standard amount of factor concentrate. Moderate short-term morbidity corresponded to more severe bleeding episodes that required twice as many doses of factor concentrate. Major short-term morbidity referred to those bleeding episodes.
severe enough to require hospitalisation. A simplified structure of the tree was reported. The time horizon of the model was the patient’s lifetime. The cycle length was one year.

Outcomes assessed in the review
The outcomes estimated from the literature were:

the rates of complete response, partial response, and failure associated with ITI;

the likelihood of annual number of minor bleeding episodes;

the annual number of minor (divided into low, average and high), moderate, and severe bleeding episodes;

the lifetime risk and rate of developing arthropathy;

the excess risk annual hazard rate for mortality; and

the success rate of haemostatic agents.

Study designs and other criteria for inclusion in the review
It was unclear whether a systematic review of the literature was undertaken to identify relevant studies. The designs of the primary studies were unclear. One of the sources was a clinical trial.

Sources searched to identify primary studies
Not stated.

Criteria used to ensure the validity of primary studies
Not stated.

Methods used to judge relevance and validity, and for extracting data
Not stated.

Number of primary studies included
Fifteen primary studies provided evidence.

Methods of combining primary studies
A narrative method appears to have been used to combine the primary estimates.

Investigation of differences between primary studies
Not stated.

Results of the review
The rates of complete response, partial response and failure associated with ITI were 80%, 5% and 15%, respectively.

The likelihood of annual number of minor bleeding episodes was 0.1 for low, 0.8 for average and 0.1 for high.

The average annual number of minor bleeding episodes was 15, ranging from 3 (low) to 27 (high).
The annual number of moderate bleeding episodes was 3.

The annual number of major bleeding episodes was 0.2.

The lifetime risk and rate of developing arthropathy was 0.75 over 15 years with inhibitor and 0.75 over 20 years without inhibitor.

Non-inhibitor patients were assigned a 2.5-fold increase in annual mortality rates compared with the general population, while inhibitor patients were assigned a 4-fold increase.

The success rate was 0.75 for activated prothrombin complex concentrates (aPCC) and 1.0 for porcine FVIII.

**Measure of benefits used in the economic analysis**
The summary benefit measure was the survival gain associated with ITI over the use of haemostatic agents. This was obtained using the modelling approach. An annual discount rate of 3% was applied.

**Direct costs**
Discounting was relevant as the lifetime costs were estimated. An annual discount rate of 3% was applied. The unit costs were presented separately from the quantities of resources used. The formula for factor consumption, which was based on inhibitor titre, patient weight and severity of bleeding episode, was reported. The health services included in the economic evaluation were factor concentrates. The perspective adopted in the study was unclear. Resource use was mainly estimated on the basis of published studies. The costs were estimated by taking the average wholesale price for all products within a category (e.g. FVIII, aPCC). The price year was not reported.

**Statistical analysis of costs**
The costs were treated deterministically.

**Indirect Costs**
The indirect costs were not considered.

**Currency**
US dollars ($).

**Sensitivity analysis**
Univariate, two-way and threshold sensitivity analyses were performed to examine the robustness of the estimated costs and benefits to variations in some model inputs. The model inputs that were varied in the sensitivity analysis were probability of success of ITI, induction costs, discount rate, price of FVIII, aPCC and porcine FVIII, and the annual rate of minor bleeding episodes. Reasonable clinical ranges of values were used.

**Estimated benefits used in the economic analysis**
The undiscounted survival gain associated with ITI over the use of haemostatic agents was 4.6 years (64.7 years with ITI and 60.1 years with haemostatic agents). The discounted survival gain was 0.85 years.

**Cost results**
The lifetime costs were $2.9 million in a patient receiving ITI and $4.6 million in a patient receiving haemostatic agents (difference $1.7 million). The excess in costs mainly arose from the decreased efficacy and higher cost of alternative haemostatic agents to treat frequent minor bleeding episodes.
Synthesis of costs and benefits
The costs and benefits were not synthesised because ITI was both more effective and less costly than haemostatic agents.

The sensitivity analysis showed that the base-case results were quite robust to reasonable variations investigated in the sensitivity analysis. If FVIII price alone increased by 78%, or the aPCC price decreased by 45%, the long-term use of alternative haemostatic agents would be favoured over ITI, although the authors noted that such price shifts were unlikely. The threshold analysis revealed also that if ITI had a success rate higher than 27%, long-term use of alternative haemostatic was dominated. The findings were not sensitive to changes in the discount rate.

Authors’ conclusions
The use of immune tolerance induction (ITI) to manage the development of inhibitors in patients with haemophilia A was a cost-effective strategy in comparison with the use of haemostatic agents, which were both more expensive and less costly over a lifetime time horizon.

CRD COMMENTARY - Selection of comparators
The selection of the comparator was clear. Haemostatic agents represented a widely used treatment option to manage the formation of inhibitory antibodies to FVIII, while ITI represented an alternative strategy. A further alternative strategy of using porcine FVIII as the initial therapeutic strategy in the sub-set of patients in which the anti-porcine FVIII titre was low was not considered, but it would not have changed the conclusions of the analysis substantially. You should decide whether they are valid comparators in your own setting.

Validity of estimate of measure of effectiveness
The effectiveness evidence came from published studies. However, it was unclear whether a systematic review of the literature had been undertaken to identify relevant studies. No information on the designs of the primary studies was reported. The methods used to extract and then combine the primary estimates were not provided. Similarly, the validity of the primary sources was not discussed. Reasonable ranges of variations were considered in the sensitivity analysis.

Validity of estimate of measure of benefit
The summary benefit measure was appropriate for detecting the impact of the interventions on the most relevant aspect of health, that is, survival. Discounting was carried out, as recommended in US guidelines, but undiscounted results were also reported. Quality of life issues were not addressed.

Validity of estimate of costs
The perspective adopted in the analysis of costs was unclear, as the authors stated that a societal perspective was adopted but the indirect costs were not considered. In fact, only the costs strictly related with the provision of ITI and haemostatic agents were considered. The unit costs were generally reported, which enhances the possibility of replicating the results of the analysis. Resource use, which was mainly estimated from the literature, reflected a key factor, namely severity of bleeding episodes. The source of the costs was reported. The costs were treated deterministically, but alternative costs were considered in the sensitivity analysis. Discounting was relevant and was appropriately applied. The impact of variations in the discount rate was also investigated. The choice of the lifetime time horizon was appropriate. The price year was not reported, which makes reflation exercises in other settings difficult. The authors stated that other costs (e.g. hospitalisation expenses) were not included because factor concentrates account for the largest part of total costs in patients with severe haemophilia A.

Other issues
The authors did not compare their findings with those from other studies. They also did not address explicitly the issue
of the generalisability of the study results to other settings. However, sensitivity analyses were performed and wide variations in model inputs were considered. This enhances the external validity of the analysis. The study referred to patients with severe haemophilia A and this was reflected in the authors’ conclusions.

**Implications of the study**
The study results supported the choice of a long-term perspective and the use of ITI to manage the development of inhibitors in patients with haemophilia A.

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**Other publications of related interest**


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