Optimising immune tolerance induction strategies in the management of haemophilia patients with inhibitors: a cost-minimisation analysis

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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.

CRD summary
The primary objective was to explore the impact of non-immunogenic rather than immunogenic bypassing agents for the control of bleeds prior to immune tolerance induction (ITI) in haemophilia patients with inhibitors. The authors concluded that recombinant activated factor VII was the preferred agent in the management of these patients before ITI, from the perspective of the UK National Health Service. The study was well conducted and satisfactorily presented, which enhances the validity of the authors’ conclusions.

Type of economic evaluation
Cost-effectiveness analysis

Study objective
The primary objective was to explore the impact of non-immunogenic, rather than immunogenic bypassing agents for the control of bleeds prior to immune tolerance induction (ITI) in haemophilia patients with inhibitors. These two classes of agents have a different impact on anamnestic response, which worsens patients’ ITI risks, which increases the need for high-dose rather than low-dose ITI.

Interventions
In one strategy, spontaneous bleeds prior to ITI were treated with a non-immunogenic bypassing agent (recombinant activated factor VII, rFVIIa), which was followed by ITI. In the other strategy, bleeds prior to ITI were treated with an immunogenic bypassing agent (activated prothrombin complex concentrate, APCC) and then followed by ITI.

In both cases, a low-dose or high-dose ITI treatment regimen was offered, depending on the patient’s risk status. A low-dose regimen was given to good-risk patients, who had a historical peak inhibitor titre of less than 200 Bethesda units (BU) and a pre-ITI titre of less than 10 BU. A high-dose regimen was given to poor-risk patients, who had a historical peak inhibitor titre of over 200 BU or a pre-ITI titre over 10 BU. High-dose ITI treatment was recombinant factor VIII (rFVIII) given at 150 International units (IU)/kg twice daily and low-dose was rFVIII given at 75 IU/kg three times weekly.

Location/setting
UK/secondary care and hospital.

Methods
Analytical approach:
This economic evaluation was based on a decision tree model with a short time horizon, which was the period from the detection of inhibitors to their elimination through ITI. The authors stated that the perspective of the UK National Health Service (NHS) was adopted.

Effectiveness data:
The clinical data were identified in a systematic review using three databases (MEDLINE, NHS EED, and DARE). The review included randomised trials, case studies, registry reports, and clinical guidelines. The eligibility and methodological quality of the studies were determined by two authors independently. The characteristics of the patient population in terms of their risk status were taken from the Immune Tolerance Registries. The key clinical assumption,
on the basis of some published evidence, was that the effectiveness of the low-dose treatment in good-risk patients was equal to that of the high-dose treatment in poor-risk patients. The key clinical input was the measure of the treatment effect, which was defined as the proportion of patients who tolerated treatment at the end of ITI.

Monetary benefit and utility valuations:
Not relevant.

Measure of benefit:
No summary benefit measure was used because the high- and low-dose regimens were assumed to be clinically equivalent when given to the appropriate patients. The key clinical outcome was the proportion of patients effectively able to tolerate treatment.

Cost data:
The economic analysis included only those costs associated with the treatment agents and these were based on UK official sources. The resource use data were derived from published sources and supplemented by authors’ assumptions. All costs were in UK pounds sterling (£) and the price year was 2008.

Analysis of uncertainty:
A threshold analysis was carried out to identify the most influential model inputs. A Monte Carlo simulation was used due to the large standard deviations (SDs) around the cost estimates.

Results
The mean cost of treatment, from detection of titres through ITI, per patient was £959,250 (SD 593,325) with APCC, and £770,834 (SD 588,951) with rFVIIa. The absence of anamnestic response in the rFVIIa arm explained 68% of the cost difference.

When considering the effectiveness of ITI, the mean cost per patient effectively able to tolerate treatment was £1,505,279 in the APCC arm and £1,196,706 in the rFVIIa arm.

The sensitivity analysis identified the unit cost and dosage of rFVIIa as the most influential model inputs, but they would have to triple in order to change the conclusions.

The probabilistic analysis indicated that the probability of the cost of an ITI being greater than £1 million was greater in patients whose bleeding episodes prior to ITI were managed with APCC compared with patients managed with rFVIIa.

Authors’ conclusions
The authors concluded that rFVIIa was the preferred strategy in the management of patients with inhibitors, before ITI, from the perspective of the UK NHS.

CRD commentary
Interventions:
The selection of the comparators was appropriate as they were the available treatments for this patient population. The dosages and administration protocols were described in detail.

Effectiveness/benefits:
The use of a systematic review of the literature was the most appropriate approach for identifying the relevant sources of data. Key details on the literature review were given, but the approach used to pool the estimates from the literature and the design of the source studies were not reported. The quality of the studies was assessed, but the results of this assessment were not reported. This limits the possibility of judging the validity of the clinical estimates. The authors stated that there was a need for randomised controlled trials to confirm their clinical assumptions.

Costs:
The analysis of costs was restricted to those of the drugs, which were valued using NHS prices. The authors reported in detail all the assumptions they made. The unit costs, resource quantities, and price year were given. Standard deviations
around the costs were calculated and they showed the variability of these estimates.

Analysis and results:
The authors justified the use of a cost-minimisation framework on the grounds of the equal efficacy of the two regimens. They also reported findings from published studies, which suggested that no differences in survival were expected given the short time horizon and the health-related quality of life was comparable between groups. These issues determined the choice of the analytic approach, which focused on the economic impact of the various treatments. The authors stated that the model structure followed the most recent UK guidelines and international consensus recommendations. The issue of uncertainty was satisfactorily investigated using both a deterministic and a probabilistic approach. The authors acknowledged some limitations of their analysis, such as the lack of strong clinical evidence in the literature, and the short time-frame.

Concluding remarks:
The study was well conducted and satisfactorily presented, which enhances the validity of the authors’ conclusions.

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Other publications of related interest

Odeyemi IA, Guest JF. Modelling the economic impact of recombinant activated Factor VII compared to activated prothrombin-complex concentrate in the home treatment of a mild to moderate bleed in adults with inhibitors to clotting Factors VIII and IX in the UK. Journal of Medical Economics 2002; 5: 119-133.

Odeyemi IA, Guest JF. Modelling the economic impact of recombinant activated Factor VII and activated prothrombin-complex concentrate in the treatment of a mild to moderate bleed in adults with inhibitors to clotting Factors VIII and IX at a comprehensive care centre in the UK. Journal of Medical Economics 2002; 5: 51-64.

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