Intravenous or intramuscular anti-HBs immunoglobulin for the prevention of hepatitis B reinfection after orthotopic liver transplantation


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
Applying long-term fortnightly intramuscular anti-HBs immunoprophylaxis (1000 IU of anti HBS, Hepatitis-B-Immunoglobulin, Behring) to prevent reinfection with HBV (hepatitis B virus) after orthotopic liver transplantation (OLT).

Type of intervention
Secondary prevention.

Economic study type
Cost-effectiveness analysis.

Study population
Patients with HBV-induced liver disease, who underwent OLT and were clinically healthy and on long-term immunoprophylaxis.

Setting
Hospital. The economic study was carried out in Berlin, Germany.

Dates to which data relate
The exact data collection dates for effectiveness and resource use data were not explicitly specified; it was only reported that the study patients received transplants between 1989 and 1995 and that the intravenously administered regimen had been standardised since 1993. The price year was not explicitly specified.

Source of effectiveness data
The evidence for final outcomes was based on a single study.

Link between effectiveness and cost data
The costing appears to have been undertaken prospectively on the same patient sample as that used in the effectiveness analysis.

Study sample
Power calculations were not used to determine the sample size. The study sample consisted of 12 patients, with an age range from 30 to 59 years, who initially received intravenous injection. 11 patients suffered from end-stage HBV-induced liver cirrhosis at the time of transplantation and one received a transplantation because of fulminant hepatitis B. All patients were offered a switch to intramuscular application, and 6 agreed to undergo the change.
**Study design**
This was a before and after study, carried out in a single centre. The duration of the follow-up was reported only as having been for several months after the study. 6 patients declined the switch to the intramuscular application, and no other loss to follow-up was reported. Consenting patients and those who refused to participate were comparable in terms of sex, age, HBV markers, and time since OLT. All patients had received continuous intravenous immunoglobulin prophylaxis beginning with 10,000 IU of anti-HBs during the anhepatic phase, and later 1000-4000 IU every 1 to 4 weeks, during the post-transplant period (2-7 years). Since 1993, the regimen was standardised to 1500 IU every 2 to 3 weeks, to keep serum antibody titers above 100 IU/L. One intramuscular injection was given to the participants two weeks before starting the intramuscular study in order to prevent overlap between the two studies.

**Analysis of effectiveness**
The principle used in the analysis of effectiveness appears to have been treatment completers only. The clinical outcomes were serum antibody titers (as determined by enzyme immunoassay (Cobas Core anti HBs EIA, Hoffmann La Roche) and recorded before intravenous application, 2 hours later, and on days 1, 3, 5, 7, 9, 11, and 13, according to the method of Wahl et al), local and systemic side effects, and reinfection.

**Effectiveness results**
The median antibody titers of both interventions in 6 patients and the comparator in 12 patients were shown in the paper as a graph. They ranged from about 900 IU/L 2 hours after injection to about 350 IU/L on day 13 after injection for the intravenous application and about 200 IU/L at both measurement points for the intramuscular application. The stability of antibody titers was sustained for 5 of the patients who continued the fortnightly intramuscular trial for several weeks after completion of the study. Peak concentrations after intramuscular injection were much lower than after intravenous application and showed little fluctuation. No sign of reinfection was observed in any of the patients during the study and for several months thereafter. Headache of varying severity was frequently reported by patients on intravenous application, whereas only one patient had headache after intramuscular immunoglobulin. Neither group experienced any other form of general or local side effects.

**Clinical conclusions**
The study findings show that, with fortnightly intramuscular application of 1000 IU of anti-HBs, reproducible and stable antibody titers above 100 IU of anti-HBs can be achieved. The side effects of intramuscular immunoprophylaxis are minimal and the method is safe.

**Measure of benefits used in the economic analysis**
No summary benefit measure was identified in the economic analysis, and only separate clinical outcomes were reported.

**Direct costs**
Costs were not discounted due to the short time frame of the cost analysis (the time frame seems to have been two weeks). Quantities were reported separately from the costs in terms of the standardised regimen used to maintain serum antibody titers above 100 IU/L. The cost analysis covered only the costs of immunoprophylaxis as fortnightly injections. The perspective adopted in the cost analysis was not explicitly specified. The date of the price data was not explicitly specified.

**Indirect Costs**
Not included.

**Currency**
US dollars ($).

**Sensitivity analysis**
No sensitivity analysis was conducted.

**Estimated benefits used in the economic analysis**
Not applicable.

**Cost results**
The cost of immunoprophylaxis when administered intravenously (1500 IU) every fortnight was $2,000 versus $800 for fortnightly intramuscular (1000 IU) anti-HBs preparations.

**Synthesis of costs and benefits**
Costs and benefits were not combined since the use of fortnightly intramuscular immunoprophylaxis was the dominant strategy.

**Authors' conclusions**
Intramuscular immunoprophylaxis offers several advantages. It permits reduction of the dose of anti-HBs, serum antibody concentrations are much more stable, and, finally, it helps to reduce substantially the high expense of post-transplantation maintenance therapy.

**CRD COMMENTARY - Selection of comparators**
A justification was given for the choice of the comparator (intravenous anti-HBS immunoprophylaxis). It was regarded as the comparator since it was considered to be usual practice in the context in question.

**Validity of estimate of measure of effectiveness**
The internal validity of the effectiveness results cannot be guaranteed due to the inherent limitations of the before and after study design and the small sample size. It is not possible to assess the degree to which the study sample was representative of the study population. The effects of the potential confounding variables (spontaneous changes in the condition or other changes that may have occurred over the course of the study) were not investigated. Consenting patients, and those who refused to participate in intramuscular application, were found to be comparable in terms of sex, age, HBV markers, and time since OLT.

**Validity of estimate of measure of benefit**
The authors did not derive a measure of health benefit. The study was therefore a cost-consequences analysis.

**Validity of estimate of costs**
Quantities were reported separately from the costs in terms of the standardised regimen used to maintain serum antibody titers above 100 IU/L. Adequate details of the methods of cost estimation were not given. The price date was not reported and it is not clear whether any relevant cost components were omitted. The currency conversion rate used was not reported. It is not clear whether charges were used or true costs.

**Other issues**
In view of the use of a before and after study design, the absence of a sensitivity analysis, and lack of detailed information on cost structure, the study results may need to be interpreted with some degree of caution. The issue of
generalisability to other settings or countries was not addressed. Appropriate comparisons were made with other studies.

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