Cytomegalovirus immune globulin after liver transplantation: a cost-effectiveness analysis


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
The study compared orthotopic liver transplant (OLT) with routine cytomegalovirus immune globulin (CMVIG) prophylaxis against CMV-associated disease, with OLT without CMVIG prophylaxis.

Type of intervention
Secondary prevention.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised patients requiring OLT. The authors did not report any other details about the study population or study sample.

Setting
The setting was secondary care. The study used data from patients in hospitals that participated in a clinical trial of CMVIG in Boston, USA.

Dates to which data relate
The effectiveness data were taken from studies published in 1993. The resource use was estimated from patients treated between 1988 and 1990. The price year was 1999.

Source of effectiveness data
The effectiveness data were derived from a review and synthesis of completed studies.

Modelling
A decision-analytic model was used to determine the incremental cost-effectiveness ratio (ICER) of CMVIG. This used a Markov simulation to estimate the long-term survival and the costs.

Outcomes assessed in the review
The probabilities used as input parameters to the model were:

- the probability of severe CMV-associated disease in the first year;
- the probability of death from severe CMV-associated disease in the first year;
- the probability of surviving severe CMV-associated disease in the first year;
the probability of mild or no CMV disease in the first year;
the probability of death from mild or no CMV disease in the first year;
the probability of surviving mild or no CMV disease in the first year;
the annual probability of hospital readmission after the first year; and
the probability of death after the first year.

**Study designs and other criteria for inclusion in the review**
The main study used was a randomised double-blind, placebo-controlled trial, details of which have been published (see Other Publications of Related Interest). This trial was used to estimate the probability data for the model, and was supplemented by additional follow-up of some of the trial patients. The life expectancy data were estimated from a longitudinal study.

**Sources searched to identify primary studies**
Not reported.

**Criteria used to ensure the validity of primary studies**
Not reported.

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

**Number of primary studies included**
Two primary studies were included in the review.

**Methods of combining primary studies**
For variables that were not statistically significantly different between the intervention and the comparator, the weighted averages of the CMVIG and placebo data from the single trial were calculated. These used the inverse of the variants as weights. The Markov model was used to combine the probability and life expectancy data. No other methods to combine the data were reported.

**Investigation of differences between primary studies**
The authors did not investigate or explain the differences between the two primary data sources, in terms of the participants, intervention, or outcome measures.

**Results of the review**
The input parameters to the model were as follows:

- the probability of severe CMV-associated disease in the first year was 0.12 for CMVIG and 0.26 for placebo;
- the probability of death from severe CMV-associated disease in the first year was 0.59 for CMVIG and 0.59 for placebo;
- the probability of surviving severe CMV-associated disease in the first year was 0.41 for CMVIG and 0.41 for placebo;
the probability of mild or no CMV disease in the first year was 0.88 for CMVIG and 0.74 for placebo;
the probability of death from mild or no CMV disease in the first year was 0.13 for CMVIG and 0.13 for placebo;
the probability of surviving mild or no CMV disease in the first year was 0.87 for CMVIG and 0.87 for placebo;
the annual probability of hospital readmission after the first year was 0.305 for CMVIG and 0.305 for placebo; and
the probability of death after the first year was 0.074 for CMVIG and 0.074 for placebo.

Measure of benefits used in the economic analysis
The measure of health benefit used in the economic analysis was life-years saved.

Direct costs
Resource quantities and unit costs were not reported separately for most of the cost items included in the analysis. The direct costs included the hospital inpatient and outpatient services and the drug costs. The variable cost data were derived from the observed resource use and service use for 66 of the 141 patients enrolled in the CMVIG clinical trial, the main source used to estimate the effectiveness. The two hospitals contributing cost data used the transition I-
Clinical Cost Manager Cost Manager cost-accounting software, which tracks the individual expenses related to each hospital according to the category. The costs included were for admission for liver transplantation, organ acquisition, the operating room, intensive care and the regular hospital room, nursing care, laboratory and radiology tests, and pharmacy costs.

The authors reported that, at the time of the CMVIG trial, the outpatient expenses were not recorded, and thus, were unavailable for patients who participated in the study. The annual outpatient costs were derived from patients who underwent OLT at the New England Medical Centre during the fiscal year 1993. The average annual expenses were $16,400 for clinic visits and immunosuppressive treatment with cyclosporin A, based on a dose of 10 mg/kg/day. The cost of CMVIG was estimated at $13,600, using 1998 wholesale drug costs for a 70-kg person over the first 4 months after transplant. The cost of readmissions was estimated at an average cost of $7,800 per year, from patients enrolled in the CMVIG trial (1993) at the New England Medical Centre. The price year was 1999. The costs were changed to 1999 US dollars using the adjusted indices of the medical care component of the US Consumer Price Index. The costs were discounted at a rate of 3% and 5% per annum.

Statistical analysis of costs
Two sided t-tests were used to compare continuous variables, while chi-squared tests were used to compare proportions. The expected costs were calculated using multiple regression analysis (SPSS/PC+ software). The following variables were assessed as potential predictors of the costs:

the length of stay before transplantation;
the cumulative length of stay for transplantation after the first year;
the drug (CMVIG or placebo);
survival status; and
the presence of one or more of the following, severe CMV-associated disease, CMV viremia, any opportunistic infection or invasive fungal disease.

Indirect Costs
No indirect costs were included in the analysis.
Currency
US dollars ($). No currency conversions were reported.

Sensitivity analysis
A one-way sensitivity analysis was conducted to assess the impact of several factors on the cost-effectiveness of CMVIG. The following factors were varied:

- the efficacy of CMVIG,
- the cost of CMVIG,
- survival in the first year and after 1-year follow-up,
- the length and quality of hospital stay, and
- the probability of severe CMVIG-associated disease.

CMVIG resulted in an undiscounted life expectancy of 11.45 years, compared with 10.56 years in the placebo group. CMVIG was associated with an additional 0.88 undiscounted life-years, and 0.65 life-years when using a 3% discount rate or 0.56 life-years when using a 5% discount rate.

Cost results
The expected first year costs were $122,300 for CMVIG recipients and $122,100 for placebo recipients. The incremental expected cost of CMVIG at 1 year was $200. The lifetime expected costs were $199,700 for CMVIG recipients and $183,900 for placebo recipients. The undiscounted, lifetime incremental expected cost of CMVIG was $15,800. The discounted, lifetime incremental expected cost of CMVIG was $11,400 when using a 3% discount rate, and $9,700 when using a 5% discount rate. The total expected costs for CMVIG were $322,000, compared with $306,000 for placebo. The undiscounted, total incremental expected cost of CMVIG was $16,000. The discounted, total incremental expected cost of CMVIG was $11,600 when using a 3% discount rate, and $9,900 when using a 5% discount rate.

The regression analysis indicated that hospital length of stay and survival were independent predictors of the cost. Severe CMV was not an independent predictor per se, but the mean length of stay of people with severe CMV was statistically significantly higher than for other patients. The costs of complications or adverse events associated with CMVIG were excluded, on the basis that there was no statistically significant difference in the rate of adverse events in the controlled trial of CMVIG.

Synthesis of costs and benefits
The costs and the benefits were synthesised by calculating an ICER (cost per life-year saved).

In the baseline analysis, the ICER of CMVIG was $17,900 per life-year saved using a discount rate of 3%.

If the estimate of efficacy for CMVIG was derived from the 5% and 95% confidence bounds, then the ICER ranged between $14,000 and $66,200 per life-year gained.

If the cost of CMVIG was varied, the authors reported that there were proportional changes in the ICERs. For example, the authors reported that the marginal cost-effectiveness ratio was $28,400 per life-year saved if the cost of CMVIG was $20,400, and $11,600 per life-year saved if the cost was $9,500.

If survival was reduced to 30% at 9 years, then CMVIG was associated with an ICER of $17,500 per life-year saved.

If the average length of hospital stay was reduced by 53% to the national average, the ICER was increased to $26,600 (3% discount rate).
The authors reported that, as long-term survival declines, the ICER for CMVIG prophylaxis becomes lower. This reflects the additional cost of long-term care, with each additional year costing $18,700.

The ICER only increased markedly (over $50,000) at low probabilities of severe CMV disease (less than 0.13).

**Authors' conclusions**

Routine prophylaxis with intravenous cytomegalovirus immune globulin (CMVIG) in patients undergoing orthotopic liver transplant (OLT) was an appropriate use of resources. It provided significant clinical benefits at a reasonable extra cost, and with a cost-effectiveness ratio comparable to that of other well-accepted medical therapies.

**CRD COMMENTARY - Selection of comparators**

The authors did not justify their choice of the placebo comparator used, but did identify other approaches used to reduce the impact of severe CMV disease. In addition, they did not describe usual care and whether this included other forms of prophylaxis or treatment for CMV disease. You should decide if no CMV prophylaxis (or placebo) is a widely used health technology in your own setting.

**Validity of estimate of measure of effectiveness**

The estimates of effectiveness for the model were derived from two primary studies. The authors have not stated whether a systematic review of the literature was undertaken, and appear to have used data from the available studies selectively. However, all the estimates of the effectiveness of CMVIG and placebo were derived from one randomised controlled trial of CMVIG and placebo. The authors did not report whether other trials had been conducted or published. The methods used to assess the validity of the studies, and to extract the data, were not reported. In addition, there were no details of the design and protocol of the primary studies used, or the patient population.

**Validity of estimate of measure of benefit**

The benefits (life-years gained) were estimated directly from the effectiveness analysis using a decision-analytic model to combine the probability, life expectancy and survival data. The authors reported the structure of the model and justified the assumptions they used. However, the did not report the methods used to validate the structure of the model.

**Validity of estimate of costs**

The perspective of the study was not reported. The authors noted that the indirect costs and the costs of the physician fees were not included in the analysis, which means that the costs were underestimated. The authors indicate that this may bias the analysis in favour of the intervention, CMVIG. The costs of inpatient care were estimated from observed data for a sample of patients enrolled in the trial used to estimate the effectiveness. This was supplemented by the actual costs for outpatient care, which were obtained from a sample of OLT patients in one hospital. Most items of resource use or unit costs were not reported separately. Both statistical and sensitivity analyses of the prices and the quantities were performed. The costs were inflated to 1999 US dollars using the adjusted indices of the medical care component of the US Consumer Price Index. The lifetime costs were discounted at rates of 3% and 5% per annum.

**Other issues**

The authors compared their findings with those from economic studies of other diseases and health care interventions. However, they did not address the issue of generalisability of the results to other settings. A number of limitations to the study were reported. One limitation was that the analysis was restricted to the overall transplant sample, with no distinction being made between serologic groups with different risks of CMV infection.

**Implications of the study**

The authors conclude that routine prophylaxis with intravenous CMVIG in patients undergoing OLT is an appropriate
use of resources, since it provides significant clinical benefits at a reasonable incremental cost. In addition, the cost-effectiveness ratio is comparable to that of other well-accepted medical therapies. Consequently, the authors propose that CMVIG should be used routinely in patients who have undergone OLT.

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