Economic evaluation of Neoral versus Sandimmune maintenance therapy for de novo liver transplant patients: results from an international randomized controlled trial

Peeters P, Kazek M, Abella I, Noble I

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 cyclosporine treatments for patients who had received liver transplantation were examined. The treatments were Sandimmune and Neoral.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The following information was obtained from the paper reporting the clinical study (see Other Publications of Related Interest). The study population comprised patients aged between 18 and 70 years, who were undergoing primary whole organ, orthotopic liver transplantation. Many exclusion criteria were reported. For example, a multiple-organ transplant, second or subsequent liver transplant, or history of malignancy. Patients were also excluded if they had been treated with cyclosporine for any indication within one month before transplantation, with an investigational drug within one month before transplantation, or with isoniazide, rifampicin, macrolide antibiotics, ketoconazole, aminoglycosides, amphotericin B, or melphalan within one week before treatment. Patients with poor renal function or renal dialysis before starting transplantation, or with a life expectancy of less than one week, were also excluded. Women who were pregnant, lactating, or not using adequate contraceptive measures were excluded.

Setting
The setting was a hospital. The economic study was conducted in Belgium, France and the UK.

Dates to which data relate
The effectiveness and resource use data were gathered from October 1994 to November 1996. The price year was not explicitly reported.

Source of effectiveness data
The effectiveness evidence was derived from a single study, which was published elsewhere (see Other Publications of Related Interest).

Link between effectiveness and cost data
The costing was conducted prospectively on a sub-group of patients that were included in the effectiveness study.
Study sample
The data below were derived from the parent clinical study (see Other Publications of Related Interest). Power calculations suggested that an overall sample of 340 patients (170 in each group) was required to detect a difference of 15% in the main outcome measure (the percentage of patients experiencing an acute rejection episode), with a power of at least 80% at a 5% significance level. This assumed a rate of 50% for the proportion of patients experiencing an acute rejection episode in the Sandimmune group. The method used to select the sample was not reported. The study sample comprised 390 patients, 196 in the Neoral group and 192 in the Sandimmune group. The mean age was 49.3 years (age range: 19 - 69) in the Neoral group and 49.0 years in the Sandimmune group. Each group contained 124 men.

Study design
This was a randomised, double-blind, parallel-group study that was conducted in 28 centres across Europe and the USA. The patients were allocated to the study groups in blocks of four patients. The method of blinding was not reported. The patients were followed for 52 weeks and no loss to follow-up was reported.

Analysis of effectiveness
The analysis of the clinical study was conducted on an intention to treat basis. The primary health outcomes were rejections, graft failure and patient survival. Kaplan-Meier estimates were used for the 52-week period. Several secondary health outcomes were reported:

the percentage of patients not receiving intravenous (i.v.) cyclosporine, but with trough levels within the target range;
the duration of i.v. cyclosporine administration until definitive discontinuation;
the number of study medication dosage adjustments;
the mean daily dose of study medication;
the mean trough levels of cyclosporine; and
serum creatinine levels.

The two groups were well balanced at baseline in terms of their demographic and clinical characteristics.

Effectiveness results
The proportion of patients remaining event free was:

for treated rejection episodes, 52.5% in the Neoral group and 46.8% in the Sandimmune group (difference: 5.7; 95% confidence interval, CI: -4.4 - 15.9);

for histologically-confirmed rejection episodes, 49.9% in the Neoral group and 46.5% in the Sandimmune group (difference: 3.4; 95% CI: -6.8 - 13.5);

for steroid-resistant rejection episodes, 86.4% in the Neoral group and 83% in the Sandimmune group (difference: 3.4; 95% CI: -4 - 10.8);

for graft failure, 93.7% in the Neoral group and 88.6% in the Sandimmune group (difference: 5.1; 95% CI: -0.6 - 10.9);

for graft loss (due to graft failure and deaths), 82.3% in the Neoral group and 80.6% in the Sandimmune group (difference: 1.7; 95% CI: -6 - 9.5); and

for death, 85.4% in the Neoral group and 85.8% in the Sandimmune group (difference: -0.4; 95% CI: -7.5 - 6.5).

Only the difference in terms of patients free of treated rejections reached statistical significance. However, in the first
weeks, most of the outcome measures were significantly better in the Neoral group. Most of the secondary outcomes were comparable at the end of the study period. In the subgroup analysis of patients managed with T-tube biliary drainage, the results favoured the Neoral group.

**Clinical conclusions**
The effectiveness study showed that patients in the Neoral group experienced fewer rejections. The proportion of those patients remaining free of treated rejections over the 52-week period was nearly significant. These favourable results were more apparent in the first weeks of treatment.

**Measure of benefits used in the economic analysis**
No summary benefit measure was used in the economic analysis. The study was therefore classified as a cost-consequences analysis.

**Direct costs**
Discounting was irrelevant because the time horizon of the study was 4 months. The unit costs were analysed separately from the quantities of resources used. The health services included in the economic evaluation were hospital stay (general ward, transplant unit and intensive care unit) and medication (Neoral, Sandimmune, tacrolimus, OKT3, ATG, ALG and methylprednisolone). The cost/resource boundary adopted in the study was unclear. The cost analysis referred to France, Belgium and the UK. Resource use was estimated using actual data gathered prospectively alongside the MILTON study. The hospital costs were derived using official accounting data from each country and personal communications for France and Belgium. The hospital data for the UK were estimated from the tariff lists of a sample of 12 hospitals. The medication costs came from average wholesale prices and pharmaceutical company prices. The price year was not explicitly reported, although most of the costs appear to have been estimated in 1995.

**Statistical analysis of costs**
Statistical tests were conducted to analyse the cost and resource use data, which were reported as average values and 95% CIs for the differences between the two treatments.

**Indirect Costs**
The indirect costs were not included in the economic evaluation.

**Currency**
The costs were reported in French francs (Ffr), Belgian francs (Bfr) and UK pounds sterling ().
In Belgium, the estimated costs were Bfr 769,780 with Sandimmune and Bfr 708,461 with Neoral (cost difference: 61,319).

In the UK, the estimated costs were 15,253 with Sandimmune and 13,720 with Neoral (cost difference: 1,533).

All of the cost differences favoured Sandimmune.

The average cost-savings were -9.09% (95% CI: -22.98 - 5.78) in France, -7.97% (95% CI: -23.06 - 8.13) in Belgium and -10.05% (95% CI: -28.06 - 8.37) in the UK.

The authors stated that the reduction in costs was mainly due to the fewer days spent in hospital and the decreased use of expensive antirejection therapy and antiviral drugs.

**Synthesis of costs and benefits**
The costs and benefits were not combined because a cost-consequences analysis was conducted.

**Authors’ conclusions**
Neoral led to cost-savings in all countries where the analysis was conducted (Belgium, France and the UK) in the first months post-transplantation, during which most of the expenses were incurred. The earlier effectiveness study had already shown some beneficial clinical effects of Neoral in comparison with Sandimmune.

**CRD COMMENTARY - Selection of comparators**
The rationale for the choice of the comparator was clear. Sandimmune represented the standard therapy, while Neoral had recently been released as a treatment for liver transplant recipients. You should decide whether they represent valid comparators in your own setting.

**Validity of estimate of measure of effectiveness**
The analysis of effectiveness used a randomised, blind clinical trial, which was appropriate for the study question. The method of randomisation was described and the authors took potential biases and confounding factors into consideration. The study groups were comparable at baseline and power calculations were performed. The study sample was likely to have been representative of the study population. Specific inclusion and exclusion criteria were reported. The basis of the analysis of the clinical study was intention to treat. These issues tend to enhance the internal validity of the analysis. The reader should note that the paper based on the clinical trial was the principal source of the data reported in this abstract (see Other Publications of Related Interest). The reporting of the effectiveness in the present study was extremely limited.

**Validity of estimate of measure of benefit**
No summary benefit measure was used in the economic analysis. The analysis was therefore categorised as a cost-consequences analysis.

**Validity of estimate of costs**
The perspective adopted in the study was not explicitly stated, although the source of the costs appears to have been the third-party payer in each country. A detailed breakdown of the cost items was reported and the unit costs were analysed separately from the quantities of resources used. Average values and CIs were reported for each category of resource used. This makes it easy to replicate the economic analysis in other settings because disaggregated data were reported. However, the cost estimates were specific to each country and the price year was not reported. Thus, reflation exercises in other settings may be difficult. Nevertheless, it seems that the aim of the study was to differentiate between the countries and to estimate the economic impact of the study treatments in each different setting. The overall validity of the cost analysis appears high.
Other issues
The authors did not compare their findings with those from other studies. They also did not address the issue of the generalisability of the study results to other settings. Sensitivity analyses were not conducted, consequently the external validity of the study was low. Although the authors focused on country-specific analyses, the results of the study were similar across the three countries. This suggested that the conclusion concerning the cost-savings obtained with Neoral was very strong.

Implications of the study
The study results suggested that Neoral is associated with lower costs and some clinical benefits in comparison with Sandimmune. The authors stated that such cost-savings are expected to be maintained over the long-term, although the results of the one-year cost analysis will be reported elsewhere.

Source of funding
None stated.

Bibliographic details

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Other publications of related interest

Indexing Status
Subject indexing assigned by NLM

MeSH
Administration, Oral; Antilymphocyte Serum /therapeutic use; Costs and Cost Analysis; Cyclosporine /administration & dosage /economics /therapeutic use; Drug Therapy, Combination; Europe; Humans; Immunosuppression /economics; Immunosuppressive Agents /administration & dosage /economics /therapeutic use; Infusions, Intravenous; International Cooperation; Length of Stay; Liver Transplantation /economics /immunology; Methylprednisolone /therapeutic use; Muromonab-CD3 /therapeutic use; Tacrolimus /therapeutic use; United States

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