Incremental cost-effectiveness analysis of intravenous ganciclovir versus oral ganciclovir in the maintenance treatment of newly diagnosed cytomegalovirus retinitis in patients with AIDS

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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
The use of ganciclovir for the treatment of acquired immune deficiency syndrome (AIDS) patients with newly diagnosed cytomegalovirus (CMV) retinitis. If the retinitis had stabilised following induction therapy with intravenous (IV) ganciclovir (5 mg/kg twice daily for 14 days, then once daily for 7 days), the patient was given oral ganciclovir (3,000 mg/day) as maintenance therapy. Maintenance therapy with IV ganciclovir (5 mg/kg per day) was the comparator since it was widely established as the preferred treatment. When the CMV retinitis progressed after maintenance therapy, the patients in both groups were given IV ganciclovir reinduction.

Type of intervention
Secondary prevention.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised AIDS patients with newly diagnosed retinitis, which had been stabilised by IV ganciclovir. Patients were excluded if they had signs or symptoms of serious gastrointestinal disease, an absolute neutrophil count below 1,000 cells/mm3 or a creatinine clearance rate of less than 70 mL/minute.

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

Dates to which data relate
The effectiveness evidence was gathered between 1991 and 1992. Resource use was estimated retrospectively, the date of the estimation was not given. The authors reported using cost data collected in 1993, 1994 and 1995. They stated that they did not adjust the costs to a common price year.

Source of effectiveness data
The effectiveness data were derived from a single study.

Link between effectiveness and cost data
The costing was carried out retrospectively on the basis of estimated resource use, as the resource use data were not collected at the time of the trial.
Study sample
In the earlier effectiveness paper, it was stated that a sample of 120 participants was sufficient to give the study 80% power to detect a difference of at least 25 days in the mean time to progression between the two treatment groups, using a two-sided test at the 0.05 level (see Other Publications of Related Interest). Initially, 161 patients were enrolled in the trial. Thirty-eight of these could not be randomly assigned to the maintenance treatment because of a variety of medical, social and administrative reasons. Of the remaining 123 patients who were randomly assigned maintenance treatment, 2 did not undertake it, the efficacy of the maintenance treatment could only be evaluated in 117 patients, and photographic evaluation could only be used in 115 patients. Of the 117 patients, 57 were randomised to IV ganciclovir and 60 to oral ganciclovir. All of those patients who attended centres participating in the trial and who met the eligibility criteria were included.

Study design
This was a randomised controlled trial in which patients who had received induction therapy of IV ganciclovir for 21 days were randomised between oral and IV ganciclovir as maintenance therapy. The trial took place at 15 centres in the USA and Canada. The patients were followed up for 20 weeks after randomisation. The assessment of fundus photographs, which provided the key results of the study, was blind. Non-blind funduscopy was also carried out.

Analysis of effectiveness
The basis of the analysis was intention to treat. The health outcomes used to assess the patients were the mean time from start of maintenance therapy to progression of retinitis, and the percentage of patients in whom CMV progression occurred. Catheter-related events, other ophthalmologic outcomes, patient survival, side effects, and the mean time from the start to the withdrawal from maintenance treatment were also recorded. At the start of the maintenance therapy, there were two significant differences between the two patient groups. The mean time elapsed since the diagnosis of AIDS was 11.0 months in the IV group and 16.8 months in the oral group, (p=0.02), and more patients in the IV group had Karnovsky scores of 30 to 60 (16% versus 2%).

Effectiveness results
Seventy-seven per cent of the IV group and 76% of the oral group experienced CMV progression. The mean time from the start of maintenance therapy to progression of retinitis (assessed by masked fundus photography) was 62 days for the IV group and 57 days for the oral group, (p=0.063). When assessed by funduscopy, the mean time to progression was 96 days for the IV group and 68 days for the oral group, (p=0.027).

From the fundus photography results, the 95% confidence interval (CI) for the difference in means was -22 to 12 days, which was not statistically significant. The 95% CI when funduscopy was used was -45 to -11 days, which was statistically significant.

There was no significant difference between the two groups for other ophthalmologic outcomes and patient survival rates.

The side effects were greater in the IV group. More neutropenia (absolute neutrophil count less than 5,000/mm3) was experienced in the IV group (37%) than in the oral group (24%), (p=0.17). Anaemia was also greater in the IV group (24%) than the oral group (15%), (p=0.08), as were IV catheter-related events (31% versus 10%, (p=0.006). Local catheter infection was 25% in the IV group and 0% in the oral group, while catheter-related sepsis was 8% (IV) and 0% (oral), respectively. More patients in the oral group terminated early (64%) than in the IV group (45%).

Clinical conclusions
The authors concluded that IV ganciclovir improved patient outcomes as it resulted in a longer mean time before progression of CMV retinitis. However, this improvement, found using the more reliable fundus photography, was not statistically significant and was associated with worse side effects.
Modelling
Kaplan-Meier curves were used to compare the mean time to progression in the two groups. A decision tree was used to model the treatment options given to patients under different conditions, in order to determine resource use.

Measure of benefits used in the economic analysis
The measure of benefit was the increase in days before disease progression.

Direct costs
The costs incurred by the hospital, the health system, patients, care givers and social services were included in the analysis. These costs were not broken down into the unit costs and resource quantities, although the costs of the different components were reported. The costs included were for placement of catheter lines, IV administration, medical personnel, the social worker and occupational therapist, laboratory procedures, medication and the patient/caregivers' out-of-pocket expenses. These costs were derived from published sources, local sources, experts' estimates and tariffs such as the Ontario Health Insurance Plan Schedule of benefits, and also from the Chedoke-McMaster Corporate Costing Model. The costs were reported in 1993, 1994 and 1995 Canadian dollars (Can$). No discounting was carried out since the costs for each patient were incurred in less than one year. The costs were not adjusted to a common price year. The authors reported that they developed a decision tree model, based on expert opinion, to estimate the quantities of resources used in treating the patients.

Statistical analysis of costs
A statistical analysis of the costs was not carried out.

Indirect Costs
The patients' time lost from work was included. The price of one day of full-time employment was obtained from Statistics Canada 1994. No discounting was carried out since the expenditures took place during one year. No price year was given.

Currency
Canadian dollars (Can $).

Sensitivity analysis
A sensitivity analysis was carried out using the range of the 95% CIs for the estimated gain in progression-free days.

Estimated benefits used in the economic analysis
Five progression-free days were gained in the IV group. The side effects of treatment were not included in the measure of benefit. The duration of follow-up was 140 days.

Cost results
Although four perspectives were adopted in the economic analysis, the baseline results for society and Ministry of Health perspectives are reported here.

From a societal perspective, the mean cost per patient was Can$12,589 in the oral group and Can$15,722 in the IV group.

From a Ministry of Health perspective, the mean cost per patient was Can$10,836 in the oral group and Can$13,428 in the IV group.
The incremental mean cost per patient was Can$3,133 from a societal perspective and Can$2,410 from a Ministry of Health perspective.

When the costs were adjusted for the fact that the oral group spent less time on maintenance therapy, from a societal perspective, the mean cost per patient in the oral group was Can$13,312 and the incremental cost per patient was Can$2,410. From a Ministry of Health perspective, the mean cost per patient was $11,383 and the incremental mean cost per patient was $2,045.

The costs of adverse effects during maintenance therapy, but not those occurring during induction or reinduction, were dealt with in the costing.

The duration of the costs measured was 99 days for the oral group and 104 days for IV group. However, the costs were also calculated under the assumption that patients were on oral ganciclovir for the same length of time that they were on IV ganciclovir.

The costs were included for the time period after progression when the patients were given a session of IV reinduction.

**Synthesis of costs and benefits**

The cost per progression-free day gained with IV ganciclovir was Can$482 from the societal perspective and $409 from the Ministry of Health perspective (assuming both groups were treated for the same length of time).

When the lower end of the CI for the differences between the mean times to progression (using the photography results) was used, IV ganciclovir ceased being more effective and oral ganciclovir became the dominant treatment. When the upper end of the CI was used, the incremental cost per progression-free day became Can$142 from a societal perspective and Can$118 from a Ministry of Health perspective.

The funduscopy results showed IV ganciclovir resulted in a cost per progression-free day of $42 from a societal perspective and Can$29 from a Ministry of Health perspective.

**Authors’ conclusions**

Intravenous (IV) therapy increased the progression-free time for the patients, but at a high monetary cost and at a high cost in terms of side effects.

**CRD COMMENTARY - Selection of comparators**

The reason for the comparator, IV ganciclovir, was clear in the original effectiveness study. It represented the best available treatment for maintenance therapy for AIDS patients with newly diagnosed CMV retinitis. You should consider whether it is a widely used treatment in your own setting.

**Validity of estimate of measure of effectiveness**

The effectiveness data were derived from a single study. The analysis used a randomised controlled trial, which was appropriate for the study question, although the original power calculations had suggested a minimum sample of 120 and at the end of the study there were complete data for only 115 patients. The study sample was representative of the study population as it included all the patients eligible for treatment. The patient groups were not completely comparable at analysis, thus introducing the possibility of confounding. The study did not make any adjustment for this.

**Validity of estimate of measure of benefit**

The estimate of benefit for IV patients was derived directly from the effectiveness analysis. The authors gave the effectiveness estimate considerable weight, despite the lack of statistical significance, and did not take into account the associated adverse side effects.
Validity of estimate of costs
From the cost perspectives adopted, all relevant resources appear to have been included in the analysis and, within each category, all relevant costs were included. The prices used for each cost component were given separately. The quantity of resources used per patient was not given, although the authors described clearly how they estimated these quantities by asking a panel of doctors detailed questions. The prices were taken from published sources, the authors’ setting and a costing model, and were also estimated.

Other issues
The authors made appropriate comparisons of their results with those of other studies. The issue of generalisability to other settings was not addressed and the authors stated that their results are applicable to Canada. The authors did not present their results selectively, but they did not justify the adjustments they made to the cost data to allow for the different number of days before progression. The authors were aware of some of the drawbacks of their study and acknowledged that a study that considered side effects and quality of life would be of more use. They did not draw attention to the lack of statistical significance of the main effectiveness result.

Implications of the study
The authors recommended further up-to-date research on maintenance therapy for CMV retinitis. Future research should examine IV foscarnet therapy, consider quality of life experiences for the patients, and collect the resource use data prospectively or at least as part of the trial. The authors were aware that there have been considerable improvements in the treatment of AIDS patients, so up-to-date research is very important.

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Other publications of related interest

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