Evaluation of techniques in prediction and diagnosis of cytomegalovirus disease

Evaluation of molecular techniques in prediction and diagnosis of cytomegalovirus disease in immunocompromised patients

A Szczepura,[1*] D Westmoreland,[2] Y Vinogradova,[1] J Fox[3†] and M Clark[1]

[1] Centre for Health Services Studies, University of Warwick, UK
[2] Department of Medical Microbiology and Public Health Laboratory, University Hospital of Wales, Cardiff, UK
[3] University of Wales College of Medicine, Cardiff, UK

* Corresponding author
† Present address: University of Calgary and Molecular Diagnostics, Canada

Executive summary

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Executive summary

Background

In individuals who have severely reduced immunity, cytomegalovirus (CMV) can cause serious and even fatal infection. Those at greatest risk from CMV infection include renal transplant recipients and patients who receive stem cell harvests or are bone marrow transplant recipients. Asymptomatic reactivation of CMV may occur with low levels of virus replication and no tissue damage. The difficulty for clinicians is to distinguish this type of innocuous presence of persistent virus from its active replication and disease production. The value of screening and diagnostic tests for CMV in different 'at risk' patient groups, and the best use of screening assays in predicting CMV disease and enabling pre-emptive therapy, represent an important area for health technology assessment.

Objectives

The objectives were to evaluate selected molecular tests in diagnosis and screening of CMV infection in immunosuppressed patients by

- measuring technical performance (test failure, sensitivity/specificity and turn-around time) for molecular methods versus the most commonly used non-molecular test (antigenaemia)
- determining the impact of CMV screening tests on diagnostic certainty and clinical management
- assessing the cost-effectiveness of CMV screening using molecular versus non-molecular tests and alternative testing protocols for the early identification of CMV infection.

Design

Clinical and cost-effectiveness were assessed through a prospective two-stage trial of CMV screening regimes in a routine service setting. Different molecular test results were fed back to clinicians in each stage, plus antigenaemia results. The technical performance of the molecular methods was assessed through an independent masked comparison of each molecular test against the established (antigenaemia) test. Scientists performing a particular test were blind to the other test results for that sample. Diagnostic and therapeutic impact were recorded prospectively for all tests, to include any effect on diagnostic certainty, changes to CMV therapy and any other reported impact on patient management. The cost of each test was estimated under different laboratory conditions.

Prospective patients undergoing CMV screening were compared with consecutive historical controls in the same unit.

Towards the end of the study, a survey of all UK virology laboratories was undertaken to identify current CMV screening practice and test preferences. In addition, all UK renal transplant surgeons and haematology transplant centres were surveyed in order to identify current clinical practice and perceptions of the benefits of CMV screening.

Setting

Study patients were recruited from University Hospital Wales (UHW), Cardiff. Staff in the Cardiff PHLS virology laboratory performed the tests.

Participants

A consecutive series of transplant patients was recruited to the prospective study over a 42-month period, totalling 98 renal and 140 haematology patients. It was planned to also recruit 40 patients with advanced HIV infection (CD4 $<100/mm^3$), but only seven were recruited owing to the success of new therapy [highly active antiretroviral therapy (HAART)]. Recruitment of AIDS patients was discontinued in agreement with the HTA programme.

A consecutive series of historical controls was identified, with 199 renal and 136 haematology patients who underwent transplants in the UHW during the 29 months prior to the prospective CMV screening trial.

Interventions

A predefined CMV screening protocol was applied to all patients in the prospective trial. Renal patients were tested every 4 weeks until ▶

16 weeks post-transplant (five tests in total). Haematology patients were tested every 2 weeks until 12 weeks post-transplant, and then every 4 weeks until 24 weeks (10 tests in total).

The assays used for CMV screening were as follows: non-molecular test, (1) pp65 antigenaemia assay; molecular tests, semi-quantitative in-house polymerase chain reaction (PCR), (2) single-round (PCR1) and (3) two-round, nested (PCR2); and qualitative commercial tests, (4) Roche Amplicor Assay (Amplicor) and (5) pp67 NASBA assay (NASBA).

Main outcomes measured

Diagnostic accuracy
Test failure rates, sensitivity/specificity values and positive predictive value (PPV) and negative predictive value (NPV) were measured for each assay.

Test costs
The laboratory cost of undertaking various CMV tests was measured and other NHS costs associated with false-positive or false-negative test results were estimated.

Clinical effectiveness
The likelihood of CMV disease and the likely impact of positive or negative test result on therapy and further investigations were recorded. On receipt of the test result, interim outcome measures were recorded to include the impact of test result on diagnostic certainty, changes to planned patient management (e.g. therapy, investigations) and perceived benefit. All definitive diagnoses of CMV disease, prescribing of CMV therapy and interim patient outcome at the end of the screening period were recorded.

Results

Diagnostic accuracy

Haematology transplant patients
All tests had a similar NPV (0.976–0.997) when used in CMV screening. Antigenaemia had the highest PPV (0.900), but a 25% failure rate. In-house PCR (first-round) had the highest PPV for a molecular test (0.815) and test failures were <1%.

Renal transplant patients
All tests had similar NPV (0.935–0.995). In-house PCR (first-round) had the highest PPV (0.965), with test failures <1%. Antigenaemia had a PPV of 0.939 in this patient group, with a 12% test failure rate.

Test costs

PCR1 is the least expensive molecular test (£7.80–13.70). Commercial tests, NASBA and Amplicor, are both more expensive (£22.50–34.70 NASBA; £23.20–29.20 Amplicor). Antigenaemia costs £12.50–27.40 depending on staff grade and batch size. Quantitative PCR (COBAS) is the most expensive at around £50 per sample.

Clinical effectiveness

Prospective study
Prospective data were collected via structured questionnaires completed by clinicians (2554 pre- and post-test). Clinical signs/symptoms when a screening test was requested were not related to CMV disease status, except for pyrexia ($p < 0.05$).

Renal clinicians were more likely ($p < 0.01$) to report that CMV screening results had been of benefit than were haematologists (72% vs 63%).

Ex ante haematology clinicians were significantly ($p < 0.01$) more likely to report that positive results would lead to a repeat CMV test request and other investigations (e.g. X-rays, CT/MRI, bronchoscopy); and to prescribing of CMV therapy ($p < 0.01$).

Recorded impacts on diagnostic certainty and patient management were relatively uncommon, but significant differences were observed between patient groups. Increases in diagnostic certainty were more likely in haematology patients: 13% haematology, 4% renal results ($p < 0.01$). Changes in patient management were even rarer, associated with <5% of test results. Initiation of CMV therapy was reported following 4% of results; further investigations following 3% results (significantly more likely ($p < 0.01$) for haematology patients); and avoidance of planned CMV therapy following <0.5% test results.

No clear link between screening test results and CMV prescribing was detected; clinicians appear to consider screening results in the context of other factors. For renal patients, 25% with CMV disease identified by screening tests were not prescribed ganciclovir and 10% with no disease received ganciclovir. For haematology patients, all those with CMV disease identified by screening were prescribed ganciclovir; 5% of negative patients also received ganciclovir. This pattern mirrors national survey responses, indicating that other factors are considered by clinicians (see national surveys below).

Historical controls
There was no evidence that the introduction of CMV screening led to reductions in CMV ▶

deaths or improved transplant success rates; one CMV-related death occurred during the screening period (haematology patient). No significant differences were detected in level of CMV disease (historical groups, 13% renal and 2.2% haematology; prospective study, 13% renal and 3.6% haematology). A significant increase was observed in the number of CMV diagnostic tests requested during the prospective screening trial.

Cost-effectiveness analysis (CEA)

Cost per positive test result

PCR1 was the most cost-effective screening test on this indicator (renal patients £116 per true positive, haematology patients £518). Antigenaemia was the least cost-effective screening test (renal patients £643 per true positive, haematology patients £2475). Antigenaemia diagnostic testing was less cost-effective than molecular (PCR1) screening on this parameter (renal patients £130 per true positive, haematology patients £1287).

When wider NHS costs were included, PCR1 remained the most cost-effective screening test (renal patients £116 per true positive, haematology £727). The nested in-house test (PCR2) was the least cost-effective of all tests owing to the high costs associated with false positives.

Incremental cost-effectiveness analysis

This confirmed that PCR1 remained the most cost-effective CMV screening test for renal and haematology patients.

Sensitivity analysis confirmed that PCR1 was the most cost-effective test for CMV screening.

Based on this outcome measure, CMV screening was more cost-effective in renal than haematology patients.

Cost per interim outcome measure

The cost per change in diagnostic certainty (laboratory costs and associated costs included) was £284 for renal and £134 for haematology patients. The cost per change in patient management was £993 for renal and £507 for haematology patients. Hence, based on these outcome measures, CMV screening appears to be more cost-effective in haematology than renal patients.

Cost per 'beneficial result' (as judged by clinicians)

PCR1 remained the most cost-effective test on this outcome measure. Cost-effectiveness ratios were calculated to be much more favourable for this measure: £16.54 per beneficial result for renal patients and £26.54 for haematology patients.

Value of screening

It was not possible to judge from these analyses whether the use of screening assays *per se* is worthwhile in either patient group.

National surveys

Laboratory testing

UK laboratories reported annual (2001) CMV test throughputs of 18–6776 samples; screening tests represented ≥ 75% of laboratory CMV workload. Some 28% of laboratories used antigenaemia and the remainder used PCR-based tests (one-third real-time quantitative PCR). Only 16% of laboratories expressed a preference for antigenaemia; the remainder preferred PCR tests, and were equally divided between real-time, other quantitative and qualitative PCR tests.

CMV screening protocols

Those reported nationally by laboratories and clinicians were similar to those introduced in the study, although testing was more frequent. For renal patients, weekly CMV screening tests (as opposed to 4-weekly) were undertaken for a period of 12–24 weeks post-transplant. For haematology patients, weekly or twice-weekly tests (as opposed to 2–4-weekly) were undertaken for 12–24+ weeks post-transplant.

Prescribing protocols

Fewer than half of renal transplant centres had a formal protocol to guide prescribing following CMV screening test results; most specify intervention if CMV disease is clinically suspected. Almost all (90%) haematology transplant centres reported a formal protocol, most requiring two positive tests before prescribing.

Individual clinician behaviour

If a patient tests positive after previously testing negative for CMV, two in three renal clinicians would prescribe for R–D+ transplant patients, one in three for other transplants (R+D–; R+D+; R–D–) [CMV serostatus (+/–); R = recipient, D = donor]. Haematologists would nearly all (80%) prescribe for an allograft patient, but only 20% for autografts.

CMV prophylaxis

Most renal clinicians (90%) would give prophylaxis to R–D+ transplants, fewer than one-quarter would prescribe for R+D+ or R+D– and none for R–D– transplants. No haematology transplant centre reported giving prophylaxis to autografts or to R–D– allografts, but 20% might give prophylaxis to other allografts.

Targeted CMV screening

Only one in three renal centres target CMV screening (all screen R–D+ transplants); 90% ▶

of haematology centres limit CMV screening (all exclude autologous transplants, 60% do not screen R–D– allogeneic transplants and the remainder screen all allogeneic transplants).

Cost-effectiveness of targeted screening protocols
Modelling outputs for the following targeted screening regimes (as reported in national surveys) show that PCR1 remains the most cost-effective test in both types of patient:

- renal patients – screening of R–D+ group only
- haematology patients – screening of allogeneic transplants only, excluding R–D–.

The impact of targeted screening in renal patients is calculated to be limited (cost per true positive will fall from £116 to £98); a greater effect is predicted in haematology patients (cost per true positive falling from £727 to £170).

Conclusions

The study findings offer some evidence that a CMV screening regime is more cost-effective than diagnostic testing alone, based on the cost per true positive detected and interim outcome such as changes in patient management. However, the study was unable to demonstrate any benefits in terms of longer term patient outcomes.

If CMV screening is introduced, the use of antigenaemia pp65 is clearly less cost-effective than the use of molecular tests.

The study identified the optimum test for CMV screening as an in-house molecular test (single-round PCR test). This test was less costly to perform and also resulted in lower costs linked to false positives and negatives than other tests. The in-house, semi-quantitative test was two to three times more cost-effective than the commercial molecular tests assessed.

The use of targeted screening (limiting CMV screening to high-risk transplants) as opposed to universal screening offers a significant improvement in the cost-effectiveness ratio for haematology transplant patients, but has limited impact in the case of renal transplants.

Implications for the health service

CMV screening using antigenaemia pp65, as reported by a number of UK laboratories, is clearly less cost-effective than the use of molecular tests. The use of targeted screening for haematology patients, as reported by the majority of UK centres, is clearly worthwhile. For renal transplant patients, targeted (as opposed to universal) screening offers limited improvements in cost-effectiveness. Although in-house tests are more cost-effective than the commercial molecular tests assessed, it may not be feasible to use them. Owing to changes in European Union legislation, in-house molecular assays used by the NHS must be CE marked if, as in the present case, molecular diagnostic units test screening samples are sent from patients in other hospitals and primary care settings. In the future, health technology assessments may need to be confined to commercially available CE-marked *in vitro* diagnostic kits. It will be a challenge for NHS providers to develop any in-house assays to a point where they can be assessed.

Recommendations for further research

Economic analyses could be expanded to model the cost-effectiveness of more frequent screening tests (as reported nationally), and screening in other 'at risk' groups. Subgroup specific disease groups should be investigated across a larger population to allow more accurate modelling of the impact of CMV screening on disease progression. Further studies of CMV screening programmes should address a range of outcome measures, including patient outcomes.

In a rapidly changing area such as this, health technology assessment requires careful thought. A 'fast track' assessment approach may be required, otherwise advances in technology may compel the use of CMV assays for which clinical and cost-effectiveness data are unavailable.

Because of changes in European legislation, widespread use of in-house molecular assays in the NHS may be difficult in the future. Thought should therefore be given to including funding for CE marking of in-house assays that are found to be cost-effective in any future health technology assessments.

Publication

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NHS R&D HTA Programme

The research findings from the NHS R&D Health Technology Assessment (HTA) Programme directly influence key decision-making bodies such as the National Institute for Health and Clinical Excellence (NICE) and the National Screening Committee (NSC) who rely on HTA outputs to help raise standards of care. HTA findings also help to improve the quality of the service in the NHS indirectly in that they form a key component of the 'National Knowledge Service' that is being developed to improve the evidence of clinical practice throughout the NHS.

The HTA Programme was set up in 1993. Its role is to ensure that high-quality research information on the costs, effectiveness and broader impact of health technologies is produced in the most efficient way for those who use, manage and provide care in the NHS. 'Health technologies' are broadly defined to include all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care, rather than settings of care.

The HTA Programme commissions research only on topics where it has identified key gaps in the evidence needed by the NHS. Suggestions for topics are actively sought from people working in the NHS, the public, service-users groups and professional bodies such as Royal Colleges and NHS Trusts.

Research suggestions are carefully considered by panels of independent experts (including service users) whose advice results in a ranked list of recommended research priorities. The HTA Programme then commissions the research team best suited to undertake the work, in the manner most appropriate to find the relevant answers. Some projects may take only months, others need several years to answer the research questions adequately. They may involve synthesising existing evidence or conducting a trial to produce new evidence where none currently exists.

Additionally, through its Technology Assessment Report (TAR) call-off contract, the HTA Programme is able to commission bespoke reports, principally for NICE, but also for other policy customers, such as a National Clinical Director. TARs bring together evidence on key aspects of the use of specific technologies and usually have to be completed within a short time period.

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Reports are published in the HTA monograph series if (1) they have resulted from work commissioned for the HTA Programme, and (2) they are of a sufficiently high scientific quality as assessed by the referees and editors.

Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search, appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

The research reported in this monograph was commissioned by the HTA Programme as project number 96/09/14. The contractual start date was in November 1998. The draft report began editorial review in March 2004 and was accepted for publication in August 2005. As the funder, by devising a commissioning brief, the HTA Programme specified the research question and study design. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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