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**Christophe Legendre[1] · Stephen M. Beard[2] · Anne Crochard[3] · Yvon Lebranchu[4]
Claire Pouteil-Noble[5] · Anke Richter[6] · Isabelle Durand-Zaleski[7]**
[1] St. Louis Hospital, Paris, France · [2] RTI Health Solutions, Manchester, UK
[3] GlaxoSmithKline, Marly le Roi, France · [4] Bretonneau Hospital, Tours, France
[5] Lyon-Sud Hospital, Pierre-Benite, France
[6] RTI Health Solutions, Research Triangle Park, N.C., USA
[7] ANAES, St. Denis la Plaine, France

The cost-effectiveness of prophylaxis with valaciclovir in the management of cytomegalovirus after renal transplantation

Cytomegalovirus (CMV) is a common herpes-related virus to which the majority of the population is exposed at some point in their lifetime. CMV is generally asymptomatic, and its impact is minimal. However, in patients who are at an increased risk of opportunistic infections, for example, due to drug-induced or infection-induced immunosuppression CMV infection can result in significant long-term health impacts through the development of symptomatic CMV diseases, which are often associated with significant morbidity and in some patient groups increased mortality [1, 2].

Patients undergoing renal transplantation are recognised as having a particularly increased risk for opportunistic CMV infection and CMV-related disease [3]. This is due primarily to the weakening of the immune systems through the use of antirejection treatments. Patients who receive an organ from a positive donor (D^+) but have had no previous CMV history (R^-) have a high risk of newly acquired infections, typically related to infection passed through the donated organ. Patients who have a previous CMV history (R^+) irrespective of the CMV history of the donor (D^+ or D^-) face the risk of reactivation of latent opportunistic infections. Of these two groups D^+/R^- patients are generally seen as having the highest risk of post-transplant CMV infection and disease.

CMV-related disease manifests itself in a number of different ways and is generally categorised as CMV syndrome (SYN) or CMV tissue-invasive disease (TID). In the case of CMV SYN the patients typically have clear evidence of CMV infection in blood samples and an associated level of symptoms which generally include fever and malaise. The presence of leukopenia, thrombocytopenia, and elevation in hepatic transminases are also used in arriving at a formal diagnosis of CMV SYN. CMV TID is defined as disease that goes beyond a general symptomatic presentation and shows evidence of localised CMV infection in tissue biopsy samples with possible signs of solid organ involvement. Therefore CMV TID is a more severe form of CMV disease and can therefore be expected to present a greater health burden to patients, requiring a higher level of healthcare resource use, in particular hospitalisation, in the management of infected patients.

The treatment of CMV disease is typically based on intravenous ganciclovir (GCV) administered daily over a 2- to 3-week hospitalisation period, with the possibility of a continued out-patient-based maintenance treatment using oral CGV over an extended 3- to 4-month period.

As CMV disease carries significant health and resource impacts, clinical management strategies that reduce the risk of CMV infection in higher risk patient groups (D^+/R^- and R^+ patients) can potentially result in significant improvements in patient outcomes and carry economic savings [1]. Previous studies have estimated the typical cost of treating a case of CMV disease in the range €16,000–21,500 (1996 conversion at £1=€0.70) in the United Kingdom [4]. Tsevat and colleagues [5] suggested additional costs of US $5,600–12,500 (1987 values) for renal patients with CMV disease.

A number of clinical management strategies have been suggested for CMV prevention in renal transplant patients; these take one of two general treatment approaches. The first option is prophylaxis-based antiviral treatment given to all high-risk patients following transplantation using drugs such as valaciclovir (VCV) or GCV. The second option is to use intensive monitoring, followed by pre-emptive antiviral treatment on identification of pre-clinical signs of CMV infection (viral shedding) which can therefore target patients prior to the potential development of CMV disease. The alternative to these active management approaches is to provide no additional preventive treatment and simply treat symptomatic CMV disease as it presents; this is commonly referred to as deferred treatment, or a 'wait-and-treat' clinical management strategy.

In this study we report the results of a decision model used to consider the relative cost and clinical effectiveness of alternative preventive strategies for CMV infection in post-renal transplantation. The model takes the perspective of the French healthcare system and is based on the results of a postal survey of current clinical practice in over 31 adult transplant centres in France. Oral prophylactic treatments based on VCV and GCV were compared to both pre-emptive treatment using intravenous GCV and a wait-and-treat strategies. The analysis considered CMV infection in two high-risk patient groups, D^+/R^- and R^+, and was conducted from the viewpoint of health-care providers in France.

Methods

Model structure

The economic model compared three preventive management strategies to a control strategy of only treating patients once full symptomatic CMV disease had fully presented (the deferred treatment strategy): (a) *prophylactic treatment* of all patients following renal transplantation using *oral GCV*, (b) *prophylactic treatment* of all patients following renal transplantation using *oral VCV*, and (c) intensive monitoring to detect CMV (infection) followed by *pre-emptive treatment* treatment using *intravenous GCV* in patients testing positive for pre-clinical CMV infection.

The model was built in Microsoft Excel and was based on a standard decision tree structure representing the follow-up of patients up to 6 months after renal transplantation (**Fig. 1**). The model structure considered the baseline risk of CMV infection in untreated patients and the risk reduction expected across each of the preventive clinical management strategies. The predicted level of CMV disease was broken down further into CMV SYN and CMV TID, allowing the model to recognise potential differences in treatment. The model structure was used to analyse the resource use and cost associated with each preventive treatment strategy, allowing for the observed reduction in the levels of CMV disease for each strategy.

Abstract

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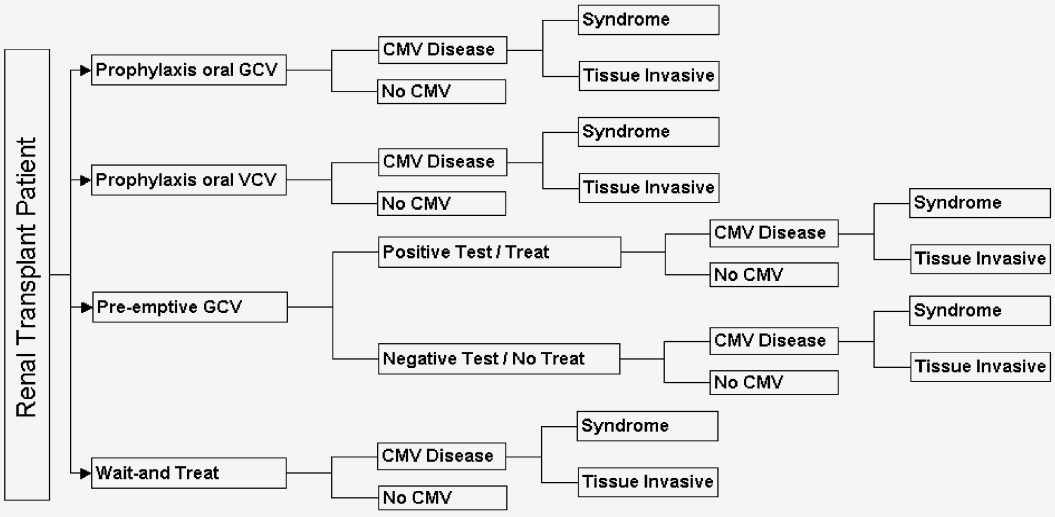
Abstract
Prophylaxis-based antiviral treatment and intensive monitoring followed by pre-emptive antiviral treatment are both commonly used management strategies to reduce risk of cytomegalovirus (CMV) infection following renal transplantation. This study employed a decision-model approach using published efficacy data and information from a recent survey of French clinical practice to consider the relative costs and outcomes associated with CMV prevention strategies for high-risk patient groups. The cost per case of treating tissue invasive and symptomatic CMV disease was estimated at €15,431 and €10,852, respectively. In the highest infection-risk patient group (positive donor with no previous CMV history) prophylactic oral valaciclovir was shown to avoid the greatest number of CMV disease cases (35 cases per 100 transplanted patients) and reduced the overall CMV-related costs per transplanted patient by around 14% over a 'wait-and-treat' baseline strategy. In contrast, intensive monitoring and pre-emptive treatment resulted in a much higher cost per transplanted patient. This analysis suggests that prophylactic treatment remains the most cost-effective approach to the management of CMV in renal-transplanted patients. Further comparative studies between prophylactic and pre-emptive treatment would be a valuable addition to the current evidence based on CMV prevention.

Keywords
Cytomegalovirus · Economics · Kidney transplantation · Valaciclovir · Prevention



Syndrome = CMV Disease with general symptomatic presetnation; including, fever and malaise

Tissue Invasive = CMV Disease with symptomatic presentation + localised infection in biopsies/organ involvement

VCV = Valaciclovir / GCV = Ganciclovir

Fig. 1 ◀ **CMV model structure**

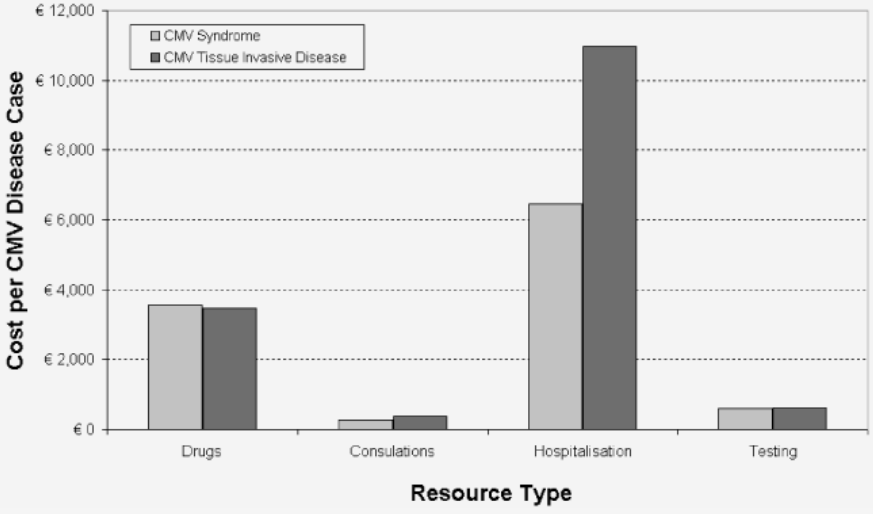


Fig. 2 ◀ **Cost of treating CMV disease**

Resource use and unit cost data

Resource use and costs were computed from the viewpoint of the French healthcare system, with a time horizon of 6 months. The clinical management strategies in the model were based on those identified in a survey of current clinic practice in French transplant centres [6]. This review involved a postal survey of 31 responding transplant centres out of the 36 existing in France (response rate 86%). The questionnaire was designed to elicit information on the typical treatment resources used to provide prophylactic and pre-emptive prevention therapy as well as the actual treatment of emerging CMV disease, based on activity in 2000. The survey results were also used to inform the development of the CMV treatment algorithms, used to populate resource use data elements of the model (**Table 1**). These data were reviewed with a French transplantation expert who was actively involved in clinical trials and has published extensively in the CMV field (C.L., 2003). Treatment costs for CMV disease were estimated separately for CMV SYN and CMV TID and were broken down into three components: initial diagnosis, primary drug-based treatment and continued maintenance therapy (to avoid potential disease recurrence).

Initial diagnosis was assumed to involve an out-patient visit and a series of standard tests, which could include; standard blood tests, antigenaemia, shell vial cultures and a polymerase chain reaction (PCR) test in a proportion of patients (approx. 25%). Primary treatment for CMV disease was based on intravenous GCV, ranging from an expected 10 days average hospitalisation for CMV SYN to 17 days for CMV TID (**Table 1**). Maintenance therapy was assumed to be provided in 34–42% of cases depending on the form of CMV disease experienced, based on the

Table 1

Primary treatment of CMV disease

	CMV syndrome		CMV tissue invasive disease		Source
	% Patients	Frequency per patient	% Patients	Frequency per patient	
Hospital days (renal)	100	10	100	17	French clinical survey
Out-patient visit	100	6	100	9	French clinical survey
Antigenaemia test	92	4	90	4	French clinical survey
Hepatic test	12	4	5	4	French clinical survey
Haemogram-platelet test	19	4	20	4	French clinical survey
PCR test	15	4	25	4	French clinical survey
Creatinine clearance testing	100	4	100	4	Clinical assumption
Ganciclovir IV 700 mg/day	97	15	100	16	French clinical survey
Ganciclovir oral 3 g/day	16	90	8	90	French clinical survey

clinical survey results. Treatment was assumed to last 8 weeks and involved regular monitoring with a 70% chance of receiving additional oral antiviral-based therapy. The model also carried an expected level of disease recurrence, set to 20% for both CMV SYN and CMV TID. As reported recurrence levels vary in the literature, we explored a range from 5% to 40% in the sensitivity analyses. Treatment on recurrence was assumed identical to the initial CMV treatment.

Information on expected resource use for the prophylactic strategies (**Table 2**) and the monitoring and pre-emptive treatment strategy (**Table 2**) was based on the clinical survey and clinical opinion. Prophylactic treatment was based on an average of 90 days treatment, using average daily doses of 3 g for GCV and 8 g for VCV, as suggested by the French clinical survey [6]. A common set of weekly follow-up monitoring and laboratory tests

Table 2

Preventive treatment for CMV infection

	% Patients	Frequency per patient (days/tests)			Source
		GCV: IV	GCV: oral, 3 g/day	VCV: oral, 8 mg/day	
Prophylaxis treatment					
• Treatment phase					
– Oral drug therapy	100	–	90	90	French clinical survey
– Out-patient visit	100	–	12	12	Clinical assumption
– Creatinine clearance test	100	–	12	12	Clinical assumption
– Antigenaemia test	55	–	12	12	French clinical survey
– Shell vial cultures	16	–	12	12	French clinical survey
– PCR test	19	–	12	12	French clinical survey
Pre-emptive treatment					
• Monitoring phase[a]					
– Out-patient Visit	100	16	–	–	Clinical assumption
– Antigenaemia	55	16	–	–	Clinical assumption
– Shell vial cultures	16	16	–	–	Clinical assumption
– PCR test	19	16	–	–	Clinical assumption
– Creatine clearance	100	16	–	–	Clinical assumption
• Treatment phase					
– Ganciclovir IV 700 mg/day	100	14	–	–	Clinical assumption
– Infusion (nurse home visit)	50	14	–	–	Clinical assumption
– Infusion (day case)	50	14	–	–	Clinical assumption
– Antigenaemia test	55	12	–	–	Clinical assumption
– Shell vial cultures	16	12	–	–	Clinical assumption
– PCR test	19	12	–	–	Clinical assumption
– Creatinine clearance test	100	14	–	–	Clinical assumption

[a] *Assumed at 16-week monitoring phase*

Table 3

Unit cost data (from: Social Security cost schedule 2003, http://www.ameli.fr/76/nabm.html; Durand Zaleski, Henri Mondor Hospital, Paris, personal communication, 2003; GERS 2002 Drug Cost Database, http://www.gie-gers.fr/)

	Unit cost (€)	Source
Hospital costs/day, renal	537.43	Henri Mondor Hospital
Day case, short infusion	396.00	Henri Mondor Hospital
Nurse home visit	18.00	Henri Mondor Hospital
Out-patient visit	23.00	Henri Mondor Hospital
Antigenaemia test	52.00	Social Security cost schedule
Shell vial cultures	39.00	Social Security cost schedule
Complete blood count	26.00	Social Security cost schedule
Chemistry panel, SMA 12	10.40	Social Security cost schedule
PCR test	65.00	Social Security cost schedule
Hepatic test	23.40	Social Security cost schedule
Haemogram-platelet test	10.40	Social Security cost schedule
Tissue biopsy	115.20	Social Security cost schedule
Creatinine clearance test	2.60	Social Security cost schedule
Valaciclovir oral 8 g/day	33.04	GERS database 2002
Ganciclovir IV 700 mg/day	74.70	GERS database 2002
Ganciclovir oral 3 g/day	52.73	GERS database 2002

Table 4

Baseline CMV risk and risk reduction data

	D^+/R^-	R^+	Source
Background risk (%)			
• CMV disease	45	6	[8]
CMV, SYN	20	4	[8]
• CMV, TID	25	2	[8]
• CMV infection risk	75		[9, 12]
Relative risk data			
• Prophylactic oral VCV	0.22	0.18	[8]
• Prophylactic oral GCV	0.35		[7]
• Pre-emptive IV GCV, SYN	0.85		[11]
• Pre-emptive IV GCV, TID	1.00		[11]

Table 5

Cost per patient of treating CMV disease (euros)

	Diagnosis, induction	Maintenance	Recurrence	Total	%
CMV SYN	8,221	822	1,809	10,852	
• Drugs	2,312	647	592	3,550	33
• Consultations	161	63	45	268	2
• Hospitalisation	5,374	0	1,075	6,449	59
• Testing	374	113	97	585	6
CMV TID	11,843	1,016	2,572	15,431	
• Drugs	2,087	799	577	3,463	22
• Consultations	230	77	61	369	2
• Hospitalisation	9,136	0	1,827	10,964	72
• Testing	390	140	106	635	4

were assumed for both prophylactic treatment strategies.

The survey provided little information on the typical resource use for a preemptive management strategy. The model therefore assumed a 16-week follow-up post-transplantation, based on a previous study of preemptive GCV therapy [7]. This mirrored the monitoring duration used in a previous model of CMV infection from the United States [4]. The model assumed a standard 14-day intravenous GCV preemptive therapy (**Table 2**) administered equally across day-case and nurse home support. Monitoring was continued for a 3-month period (as with prophylactic treatment). The model applied a set of unit cost data (**Table 3**) to resource use estimates to calculate the overall cost of CMV disease treatment and preventive management. Costs were computed in 2003 euros. Drug costs were taken from the GERS database, as a standard pharmaceutical cost (GERS drug cost database, 2002: http://www.gie-gers.fr/). Diagnostic costs were based on the social security cost schedule (Social Security cost schedule, 2003: http://www.ameli.fr/76/nabm.html). Hospitalisation costs were based on a French transplant centre and were estimated using the hospital's accounting system, excluding all costs of tests and drugs (D. Zaleski, Henri Mondor Hospital, Paris, personal communication, 2003).

Treatment effect data

The model used background rates for developing symptomatic CMV disease from a placebo-controlled clinical trial of oral VCV [8]. This trial was conducted over 600 patients across both D^+/R^- and R^+ patient groups. Clinical endpoints 6 months after renal transplantation were reported separately for CMV SYN and CMV TID. In the untreated D^+/R^- patients the overall risk of CMV disease was reported at 45% (**Table 4**), split into 45% as CMV SYN and 55% as CMV TID. In R^+ patients the background risk was much lower, at 6%, of which one-third was related to CMV TID (**Table 4**). Three smaller clinical trials were also considered for baseline risks [9, 10, 11]. However, none reported risk data for the separate risk groups, and none used a true placebo arm comparator,

with acyclovir used at therapeutic doses in some studies.

The model considered the treatment efficacy of each preventive strategy by applying a relative risk to the baseline risk of CMV disease. No direct trial comparisons were identified for prophylactic oral VCV and oral GCV. The model was therefore populated with relative risk data taken from two separately reported clinical studies. Treatment effect data were based on reported intention to treat outcomes and therefore included treatment drop-outs, including those for any treatment adverse events. The Lowance et al. [8] study was used to determine prophylactic oral VCV as this provided a direct comparison of treatment to a 'wait-and-treat' strategy, based on the deferred treatment of CMV disease. The trial reported an overall relative risk of CMV disease of 0.22 in D^+/R^- patients and 0.18 in R^+ patients. This overall level of risk reduction was assumed to hold for both CMV SYN and CMV TID (**Table 4**).

At the time of model development (2002), a review of the literature found no published clinical study comparing oral GCV to a placebo (no treatment) arm, nor did it identify any clinical trial reporting risk data for separate patient groups (D^+/R^- and R^+). Of the four trials identified one combined oral and intravenous treatment, and another used therapeutic levels of acyclovir. The model therefore derived relative risk data from a study using a subtherapeutic level of acyclovir (400 mg/day) over a 12-week period in a mixed group of renal transplant patients [11]. In the absence of patient-group level data overall relative risks were applied equally in the D^+/R^- and R^+ patient groups for both CMV SYN and CMV TID.

The model used two specific parameters to model the effectiveness of pre-emptive treatment. First, the background level of CMV pre-clinical infection in high-risk patients was set to 75% based on two published studies reporting pre-clinical infection identified during an intensive monitoring phase, including PCR testing [9, 12]. Kletzmayr and colleagues [9] compared the CMV infection level in untreated D^+/R^- patients to that in longer term oral GCV therapy over a 1-year period; CMV infection was noted in 75% of cases. Jung and colleagues [12] compared oral pre-emptive GCV to standard GCV prophylaxis in a mixed group of D^+/R^- and R^+ renal transplant patients and, again, included antigenaemia pp65 and PCR testing as part of the monitoring phase. CMV infection was again noted in 75% of cases. The model used the infection rate to back-calculate expected conversion rates to CMV disease using the suggested background placebo levels of disease in the model (**Table 4**). A small 2% risk of CMV disease after no previous evidence of CMV infection was used in the model [13].

At the time of developing the model there were only limited published clinical data on the effectiveness of pre-emptive treatment strategies for CMV disease in renal transplantation. A search identified only two studies reporting the clinical efficacy of pre-emptive GCV therapy after the development of pre-clinical infection [7, 12]. The study by Brennan and colleagues [7] was the only one to compare directly to a patient group receiving no preventive treatment. Pre-emptive intravenous GCV treatment was given to 14 patients following positive CMV tests based on PCR and shell vial culture. Outcomes were compared to those in 19 viraemic patients who had deferred CMV

Table 6

Cost of preventive treatment per treated patient (euros)

	Prophylaxis		Preemptive
	Oral GCV	Oral VCV	IV GCV
Total	5,619	3,847	6,159
Drugs	4,746	2,974	1,494
Consultations	276	276	3,266
Hospitalisation	0	0	0
Testing	597	597	1,399

Table 7

Baseline cost and outcomes per transplanted patient

	D^+/R^-		R^+	
	Cost (€)	Patients free of CMV disease (%)	Cost (€)	Patients free of CMV disease (%)
Baseline: deferred CMV treatment[a]	6,017	55	742	94
Prophylaxis: oral VCV	5,171	90	3,981	99
Prophylaxis: oral GCV	7,725	84	5,879	98
Pre-emptive: IV GCV	10,241	58	5,642	95

[a] *Costs and proportion of untreated renal transplanted patients free of CMV disease*

Table 8

Cost-effectiveness per transplanted patient compared to deferred treatment [*superior* treatment has both higher incremental clinical benefits and lower overall cost than the treatment comparator (baseline)]

	Incremental cost (€)		Avoided CMV cases		Cost per CMV case averted (€)	
	D^+/R^-	R^+	D^+/R^-	R^+	D^+/R^-	R^+
Baseline: deferred CMV treatment	6,017	742	0.55	0.940		
Prophylaxis: oral VCV	–846	3,239	0.35	0.049	Superior	65,829
Prophylaxis: oral GCV	1,708	5,137	0.29	0.039	5,840	131,718
Pre-emptive: IV GCV	4,225	4,900	0.03	0.005	142,605	927,981

disease treatment (a 'wait-and-treat' strategy). The study found that 40% of pre-emptive treated patients experienced symptomatic CMV SYN, compared to 47% of the deferred treatment group (a crude relative risk of 0.85). The small number of patients meant that no statistically significant difference in CMV TID rates was found (only one case was reported in each patient group). The model therefore assumed a relative risk of 1 for CMV TID. Also CMV clinical outcomes were not broken down my patient risk group, with the trial dominated by R^+ patients (31 R^+ and 5 D^+/R^-); therefore interpretations into D^+/R^- based comparisons need to be taken with some care.

Economic analysis

The economic analyses brought together the average costs of treating CMV disease and each preventive clinical management strategy together with background disease rates and relative risks to provide estimates of the following outcomes: (a) overall treatment-related cost for preventing and treating CMV disease, (b) overall cost difference for each prevention strategy compared to deferred treatment, and (c) clinical benefit of each prevention strategy (in terms of the avoided CMV disease cases compared to a deferred treatment approach). These analyses were conducted separately for the D^+/R^- and R^+ patient groups. As the time scale of the model was less than 1 year, the model did not include any discounting of either cost or clinical benefits.

Results

The cost for treating CMV SYN and CMV TID was estimated, respectively, at €10,852 and €15,431 per patient (**Table 5**). The majority of these costs were due to hospitalisation during initial diagnosis and treatment, in particular for CMV TID (**Fig. 2**). The estimated raw cost per treated patient of providing a preventive treatment for CMV disease are summarised in **Table 6**. These data show oral VCV prophylaxis having a lower cost than oral GCV due to the difference in drug cost, with other costs remaining the same over the 90-day treatment period. Pre-emptive treatment remained the most costly strategy on a per treated patient basis (**Table 6**). Lower intravenous GCV drug costs and the shorter duration of treatment were offset by higher intravenous administration costs and the need for nursing support, either at home or as day-case clinic.

The modelled analyses then focused on the cost and effectiveness of each of the preventive management strategies, combining the raw costs of preventive treatment together with cost offsets from avoided CMV infection and disease.

Cost effectiveness

D^+/R^- patients

Prophylactic treatment with oral GCV in D^+/R patients increased the cost per transplanted patient to €7,725 vs. €6,017 under deferred treatment (**Table 7**). However, prophylactic oral VCV reduced treatment-related costs by around 14%, reflecting avoided CMV cases and lower drug cost for oral VCV. The clinical effectiveness results confirmed that all three preventive treatment strategies increased the proportion of patients who remained free of CMV disease following renal transplantation (**Table 8**). Prophylactic treatment appeared to provide the greatest level of protection against CMV infection, with oral VCV treatment having a 6% higher absolute disease-free rate than oral GCV prophylaxis (90% disease-free vs. 84% disease-free).

The cost-effectiveness comparison to a baseline of deferred treatment (**Table 8**) showed:

- Prophylactic oral VCV was superior to the other preventive treatment strategies and deferred treatment, with lower levels of CMV disease and a reduction in treatment-related costs.
- Prophylactic oral GCV resulted in additional treatment-related cost of €1,708 per transplanted patient (cost per avoided CMV disease case of €5,840).
- Preemptive intravenous GCV had slightly fewer CMV disease cases over deferred treatment, at an overall increase of €4,225 per transplanted patient in treatment-related costs.

The economic analysis therefore suggests that prophylaxis remains the most clinically and economically effective management approach for CMV prevention in high-risk D^+/R^- patients. Oral VCV provided additional clinical advantages over oral GCV at a reduced cost and therefore was superior to all other preventive treatment strategies.

R^+ patients

All three preventive treatment strategies increased the cost per transplanted patient over deferred treatment in R^+ patients (**Table 7**). The lowest overall treatment cost for a preventive strategy was for prophylactic oral VCV. The clinical effectiveness results confirmed that all three preventive treatment strategies increased the proportion of patients who remained free of CMV disease following renal transplantation (**Table 7**). Prophylactic treatment appeared to provide the greatest level of protection against CMV infection, with oral VCV treatment having a 1% higher absolute disease-free rate than oral GCV prophylaxis (99% disease-free vs. 98% disease-free).

The cost-effectiveness comparison to a baseline of deferred treatment (**Table 8**) showed:

- Prophylactic oral VCV had lower levels of CMV disease over deferred treatment, with an overall increase in treatment-related costs of €3,239 per transplanted patient (a cost per avoided CMV disease case of €65,829).
- Prophylactic oral GCV had lower levels of CMV disease cases over deferred treatment, with an overall increase in treatment-related costs of €5,137 per transplanted patient (a cost per avoided CMV disease case of €131,718).
- Preemptive intravenous GCV therapy had slightly fewer CMV disease cases over deferred treatment, with an overall increase in treatment-related costs of €4,900 per transplanted patient (a cost per avoided CMV disease case of €927,981).

The economic analysis therefore suggests that prophylaxis for preventing of CMV disease is the most clinically effective

Table 9

Sensitivity analysis for oral prophylactic management of CMV [*superior* treatment has both higher incremental clinical benefits and a lower overall cost than the treatment comparator (baseline)]

	D^+/R^-				R^+			
	Change in parameter value	Additional cost (€)	Avoided CMV cases	Cost per avoided case[a]	Change in parameter value	Additional cost (€)	Avoided CMV cases	Cost per avoided case[a]
Baseline results: prophylactic VCV vs. deferred CMV treatment	–	–846	0.35	Superior	–	3,239	0.05	65,829
Cost of CMV cases	–18% –50%	0 1,501	0.35 0.35	Cost threshold 4,275 –	–50% +563%	3,543 0	0.05 0.05	72,011 Cost threshold
Cost of VCV	+29% +50%	0 618	0.35 0.35	Cost threshold 2,325 –	–50% –	1,755 –	0.05 –	35,671 –
Relative risk (oral VCV)	0.35 0.52	–64 959	0.29 0.22	Superior 4,440	0.35	3,365	0.04	86,280
Reduced level of extended hospitalisation for CMV disease	0 days SYN, 7 days TID	1,418	0.35	4,639	0 days SYN, 7 days TID	3,556	0.05	72,279
Baseline results: prophylactic oral VCV vs. prophylactic oral GCV	–	–2,554	0.06	Superior	–	–1,898	0.01	Superior
Recurrence level	40% 5%	–2,685 –2,456	0.06 0.06	Superior Superior	40% 5%	–1,919 –1,882	0.01 0.01	Superior Superior
Maintenance rate	60% 20%	–2,591 –2,523	0.06 0.06	Superior Superior	60% 20%	–1,905 –1,893	0.01 0.01	Superior Superior
Cost of CMV cases	–100%	–1,772	0.06	Superior	–100%	–1,772	0.01	Superior
Cost of VCV	+50% +86%	–1,071 0	0.06 0.06	Superior Cost threshold	+50% +64%	–412 0	0.01 0.01	Superior Cost threshold
Baseline risk of CMV disease	60% –	–2,815 –	0.08 –	Superior –	20% 2%	–2,192 –1,814	0.034 0.003	Superior Superior
Relative risk (oral GCV)	0.21	–1,712	–0.004	380,430	0.21	–1,794	0.002	Superior
Reduced level of extended hospitalisation for CMV disease	0 days SYN, 7 days TID	–2,177	0.06	Superior	0 days SYN, 7 days TID	–1,832	0.01	Superior
Baseline results: prophylactic VCV vs. preemptive intravenous GCV	–	–5,071	0.32	Superior	–	–1,661	0.04	Superior
All intravenous GCV administered at home	100%	–3,086	0.32	Superior	100%	324	0.04	7,376
Background CMV infection level	90% 50% 45%	–5,827 –3,811 –3,559	0.32 0.32 0.32	Superior Superior Superior	90% 50% 45%	–2,417 –401 –149	0.04 0.04 0.04	Superior Superior Superior
Background CMV disease level	80% 70%	–8,196 –7,303	0.57 0.50	Superior Superior	20% 10%	–3,081 –2,067	0.14 0.07	Superior Superior
Relative risk (preemptive intravenous GCV)	0.85 0.40 0.21	–4,668 –2,088 –707	0.28 0.08 0.00	Superior Superior Cost threshold	0.85 0.40	–1,629 –1,288	0.04 0.02	Superior Superior
Cost of CMV cases	+50% –100%	–7,074 –1,064	0.32 0.32	Superior Superior	50% –100%	–1,960 –1,664	0.04 0.04	Superior Superior
Reduced level of extended hospitalisation for CMV disease	0 days SYN, 7 days TID	–2,998	0.32	Superior	0 days SYN, 7 days TID	–1,378	0.04	Superior

management approach in high-risk R^+ patients. Oral VCV provided additional clinical advantages over oral GCV, at a reduced cost. Prophylactic VCV is thus superior to all other active preventive treatment strategies. However, all prevention strategies had significant additional cost over deferred treatment, which combined with the low level of CMV infection assumed in this patient group, created high cost per avoided CMV case values.

Sensitivity analyses

A range of simple sensitivity analyses were conducted altering the value of individual parameters in the model to consider the degree of impact that this had on the overall additional costs and benefits of preventive treatment strategies.

D^+/R^- patients

Prophylactic oral VCV in D^+/R^- patients remained the superior preventive management strategy to deferred CMV treatment for the majority of changes made to cost and clinical parameters (**Table 9**). The cost of treating a CMV case had to reduce by at least 18% before prophylactic oral VCV became a more costly option. Oral VCV remained superior even when the costs of CMV cases were ignored. Under baseline conditions oral VCV prophylaxis avoided approx. 35 CMV cases per 1,000 transplant patients treated. Setting the relative risk of VCV equal that of oral GCV (0.35) resulted in 29 avoided CMV cases per 1,000 patients, at a similar overall cost. In fact, the relative risk of VCV would have to increase to around 0.52 before the cost per avoided case reached levels above €4,500 vs. deferred treatment.

The analysis showed that prophylactic oral VCV remained superior to prophylactic oral GCV for the majority of changes made to the model's cost parameter values (**Table 9**). When alternative relative risk data were taken for oral GCV (0.21), a small clinical advantage in favour of GCV was observed (4 avoided cases per 1,000 patients treated). However, the additional costs of GCV remained, leading to a cost per avoided CMV case over VCV of around €380,430. Therefore even with alternative relative risk data oral VCV remained the more cost-effective strategy.

Prophylactic oral VCV remained superior to preemptive treatment, even when the costs of treating CMV disease were completely ignored, CMV infection rates were set to equal the CMV disease rates (assuming all infection results in symptomatic disease if untreated), or the relative risk of CMV disease from pre-emptive treatment was as low as 0.21 (**Table 9**).

An additional set of sensitivity analyses considered a scenario of reduced levels of additional hospitalisation as a result of CMV disease. In this case we assumed no additional days for SYN and 7 days for TID (vs. baseline assumptions of 10 and 17 days, respectively). This changed the cost effectiveness direction only in the comparison of VCV and GCV prophylaxis. VCV became more costly as an option; however, the cost per avoided CMV case remained below €5,000.

The overall message from the D^+/R^- sensitivity analysis is that the superiority of oral VCV prophylaxis over other preventive treatment strategies remains robust to large variations in both cost and clinical efficacy parameter values.

R^+ patients

Prophylactic oral VCV provided a clinical advantage over deferred treatment in R^+ patients. However, the low level of expected CMV disease in R^+ patients (6% [8]) led to an increase in the cost per patient of around €3,239 at baseline. This additional cost reduced to around €2,935 when the cost of treating CMV disease was increased by 50%.

The analysis showed that prophylactic oral VCV remained superior to prophylactic oral GCV for the majority of changes made to the model's parameter values. Even when the costs of CMV cases were reduced to zero, the lower drug costs of VCV remained superior. When relative risks for GCV were based on data from Ahsan et al. [14] (set at 0.21), VCV remained more effective and cost saving.

Prophylactic oral VCV remained superior to a preemptive strategy for the majority of changes made to the parameter values. When all preemptive treatment was assumed to take place at home, the prophylactic VCV and preemptive intravenous GCV strategies became cost equivalent. However, there remained a clear clinical advantage to prophylactic therapy. The model suggests that prophylaxis remains the most effective method to prevent CMV disease, and the lowest cost preventive strategy (other than deferred treatment).

The overall messages from the R^+ sensitivity analysis are that: (a) the wait-and-treat has a lower cost but is also less effective than preventive strategies, and (b) the superiority of oral VCV prophylactic over other preventive treatment strategies remains robust to large variations in both cost and clinical efficacy parameter values.

Discussion

Our model-based analysis of French patients at increased risk of CMV infection following renal transplantation suggests that preventive treatment avoids significant levels of CMV disease over a default strategy of deferred treatment. This is particularly true for D^+/R^- patients. The level of background CMV infection risk has a strong impact on the relative cost-effectiveness of alternative preventive treatment strategies. At levels of risk for CMV disease around 45% (as suggested for D^+/R^- patients [8]) the cost offsets from avoided CMV cases resulted in either an overall cost saving or a small level of cost per avoided case for prophylactic treatment. However, the background level of risk suggested by Lowance et al. [8] for R^+ patients was much lower than this, approx. 6%. Therefore the opportunity to avoid CMV cases in this case is much reduced, and the additional costs of prophylactic treatment begin significantly to dominate any potential cost-savings. It would be extremely helpful if additional studies were available to quantify further the underlying risks of CMV disease in renal transplant patients as we found few data in this area, particularly that which differentiates on the basis of severity of disease.

We also found only limited data in the published domain on the clinical effectiveness of pre-emptive treatment, and the reports that were identified showed only a small treatment effect compared to oral prophylaxis with either GCV or VCV. Also, these studies had varying definitions of pre-emptive strategy that may not di-

rectly translate into expected clinical practice in France. For this reason and due to the limited sample size in this study (fewer than 40 patients) it is difficult to draw any firm conclusions from the model with respect to the relative costs and benefits of prophylactic over pre-emptive treatment. Based on the data that we currently have on pre-emptive treatment, however, the model and sensitivity analysis suggest that prophylaxis is likely to avoid a greater number of CMV cases and have a much lower associated overall cost.

A recent study, published since completion of this model analysis, highlighted that under deferred treatment a significant proportion of patients who experienced CMV disease (60%) did not have a PCR positive test before disease onset [15]. Background rates of CMV disease were 49% and CMV infection 66% (similar to the values used in our analysis). On this basis the authors concluded that a prophylactic strategy would be clinically more beneficial than a pre-emptive approach. It is therefore likely that further research will be required before pre-emptive therapy can be considered as a potential alternative to prophylactic management in renal transplantation.

The modelled analysis has a number of obvious limitations. First, it must be stressed that the results are specific to the French health-care system, and that cost impacts may vary when considered for alternative healthcare settings. Second, we did not consider the potential impact of CMV disease on the risk of acute and long-term graft rejection in the analyses, which would further increase the cost advantage of avoiding a CMV infection. We also did not cover the possibility that preventive treatment may in fact simply delay the cases of CMV rather than avoiding them. Third, there is also evidence from the study by Lowance et al. [8] that avoiding CMV infections can also carry additional benefits from reductions in other opportunistic infections, again not included in the model. Therefore the true health-care cost of a CMV infection is likely to be greater than that used in the model. The model also takes no account resource impact of any treatment-related toxicity outside of the health-care resources indicated in the clinical survey for the general treatment of patients. A recent trial-based economic analysis of prophylactic VCV [16] showed similar cost savings per patient over deferred therapy in D^+/R^- patients (€1,484) but a lower additional cost per patient in R^+ patients (€476). This, again, suggests a greater cost impact of CMV disease than that considered in the model.

Finally, in the absence of in-trial direct comparisons the data on clinical efficacy were necessarily drawn from a range of individual clinical studies for each of the prevention strategies considered. However, a recently published retrospective clinical comparison of prophylactic oral VCV and oral GCV in 150 post-transplant patients (83% R^+) suggests that there is likely to be equivalence in efficacy between these oral treatments [17]. The study also highlighted the significantly lower drug costs of oral VCV (a difference of US $2,000). The 6-month risk of CMV infection in VCV treated D^+R^- patients was comparable to levels reported by larger preventive therapy study of Lowance et al. [8], at 16%. However, CMV levels in R^+ patients were considerably higher than those observed by Lowance et al. (7% vs. 1%).

Similar conclusions of equivalence were drawn by another recently published prospective comparison [18], again, in a small sample (n=38) of predominantly R^+ patients (95%). The second of these studies also suggested a cost equivalence in CMV-related expenditure for oral VCV and GCV (approximately €3,600–3,700 per treated patient, compared to €4,997 for differed therapy), representing an approximate 25% cost saving over deferred treatment, similar to that in our analysis of GCV. However, it must be stressed that the sample size is small in this case and restricted mainly to R^+ patients, with wide variation in costs observed.

Conclusion

The risk of CMV infection and disease represents a significant health issue in patients undergoing renal transplantation, and current clinical management strategies to deal with this situation can vary greatly across clinical centres. Prophylactic treatment based on oral drugs such as VCV and GCV provides an optimal treatment strategy for patients at a higher risk of infection. Available published clinical evidence demonstrates that oral prophylaxis with VCV provides a greater level of clinical effectiveness and at a lower overall cost than that with GCV. Further head-to-head studies of alternative preventive clinical management strategies in renal transplant patients are need and should cover all potential oral therapies for CMV prevention (including VCV, GCV and the GCV prodrug valganciclovir). Ideally these studies would be designed to include the collection of full health-care resource use and quality of life data in order to confirm both the economic and clinical profiles of CMV prevention strategies following renal transplantation.

Corresponding author

Stephen M. Beard

RTI Health Solutions, Manchester, UK
e-mail: sbeard@rti.org

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