Treatment of Ganciclovir-Resistant Cytomegalovirus in Adult Solid Organ Transplant Recipients
Caught Between a Rock and a Hard Place?

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Learning Objectives:

1. Describe the impact of cytomegalovirus infection and disease following solid organ transplantation and the current practice methods for prophylaxis and treatment.
2. Define the mechanisms and risk factors associated with the development of antiviral-resistant cytomegalovirus.
3. Explain when antiviral resistance should be suspected in the clinical setting and what diagnostic tests can be used for confirmation.
4. Evaluate the treatment options for ganciclovir-resistant cytomegalovirus infection and disease.
Cytomegalovirus

I. Epidemiology

a. Cytomegalovirus (CMV) is a member of the human herpesviruses
   i. Transmitted from infected individuals to others through direct contact with bodily fluids
b. Evidence of prior exposure to CMV is present in about two-thirds of the United States population
   i. Immunocompetent individuals

   - First time patient is infected with the virus
   - Asymptomatic or non-specific viral illness
   - Easily overcome by the host immune system

   - Established in individuals following primary infection
   - Latency of virus maintained primarily via cell-mediated immunity
   - Reservoirs for reactivation and spread of infection when immune system impaired

   Figure 1. Stages of initial CMV infection in immunocompetent host

ii. Solid organ transplant (SOT) recipients
   1. CMV is the most common infection leading to major complications after transplantation
      a. Rate is highly variable on type of transplantation, presence of associated risk factors, and the use of prolonged prophylaxis
   2. CMV is a major cause of morbidity and mortality
      a. Increased incidence of rejection and crude mortality among SOT recipients who have CMV disease compared to those who do not
   3. Growing rates of CMV antiviral resistance becoming an increased concern
      a. Association with poor clinical outcomes
      b. Lack of alternate antiviral treatment options

II. Definitions

a. CMV infection
   i. Evidence of CMV replication regardless of symptoms
b. CMV disease (see Table 1)
   i. Evidence of CMV infection with attributable symptoms
      1. CMV syndrome
      2. Tissue invasive disease
         a. Most severe form of CMV disease
         b. Transplanted allograft is commonly involved
         c. Biopsy required for diagnosis
   
   c. Latent CMV
      i. Virus exists as closed circular DNA
      ii. Virus reactivation induced by many factors present in the transplant recipient
         1. Therapy with antilymphocyte antibodies and cytotoxic drugs
         2. Allogeneic reactions
         3. Systemic infection and inflammation
III. Manifestations\textsuperscript{1,4,6} (see Table 1)

a. Direct effects
i. Caused by viral infection itself

b. Indirect effects
i. Viral infection results in modification of the host immune system
   1. Immunosuppressive, immunomodulatory, and inflammatory changes
   2. Cytokine and growth factor response to viral replication

| Table 1. Direct and Indirect Effects of Cytomegalovirus Infection\textsuperscript{1,4} |
|---------------------------------|-----------------|-----------------|
| **Direct Effects**              | **Indirect Effects** |
| CMV Syndrome                   | Tissue Invasive Disease | Acute rejection |
| - Fever                        | - Colitis         | - Chronic rejection |
| - Malaise                      | - Pneumonitis     | - Bacterial, viral, fungal infections |
| - Weakness                     | - Hepatitis       | - Mortality      |
| - Myalgias/arthralgias         | - Nephritis       |                 |
| - Leukopenia                   | - Gastroenteritis |                 |
| - Thrombocytopenia             | - Retinitis       |                 |

Assessing the Transplant Patient

I. Pretransplant assessment\textsuperscript{1,2,10}

a. Risk factors for development of posttransplant CMV infection and disease
   i. Donor/recipient CMV immunoglobulin G (IgG) serostatus
      1. Greatest risk factor for development of CMV disease (see Table 2)
         a. Overall rate of CMV infection and disease among CMV naïve recipients receiving seropositive organs is approximately 56% to 68%
      2. Measure anti-CMV IgG before transplantation
         a. Indicates prior exposure to CMV
         b. Performed on both the organ donor and recipient
         c. Recorded as Donor $\pm$/Recipient $\pm$ (D$\pm$/R$\pm$)
         d. Determines pharmacologic prophylactic strategy

| Table 2. Risk Stratification Based on Donor and Recipient Serostatus\textsuperscript{1,2} |
|---------------------------------|-----------------|-----------------|
| **Donor status**                | **Recipient status** |
| High risk                       | +               | -               |
| Moderate risk                   | +/-             | +               |
| Low risk                        | -               | -               |

ii. Degree of immunosuppression
   1. Small bowel/heart/lung $>$ kidney/pancreas $>$ liver
   2. Lung and small bowel considered to be at highest risk

iii. Use of lymphocyte-depleting agents
   1. Alemtuzumab, antithymocyte globulin, rituximab

iv. Host factors
   1. Age, comorbidity, leukopenia and lymphopenia, genetic factors

v. Others
   1. Cold ischemia time, critical illness, stress
II. Posttransplantation assessment and monitoring
   a. Viral load testing
      i. Important aid for diagnosing disease and monitoring response to therapy
      ii. Antigenemia assay
         1. Detects pp65 antigen in CMV-infected peripheral blood leukocytes
            a. Reported as positive cells per 200,000 leukocytes
         2. High specificity (99%)
         3. Limitations
            a. Poor sensitivity
            b. Labor intensive
            c. Limited utility in patients with leukopenia
               i. Need an ANC ≥1000 cells/mL
            d. Lack of standardization
         4. Mostly replaced by polymerase chain reaction
      iii. Quantitative nucleic acid testing (QNAT) by polymerase chain reaction (PCR)
         1. Preferred method of diagnosis and monitoring of CMV infection and disease
            a. Increased precision, faster turnaround time, and high sensitivity and specificity
               (94% and 92%, respectively)
         2. Measures viral load
            a. Reported as copies per milliliter
            b. Must be aware of institution-specific limit of detection (LOD) and limit of quantification (LOQ)
               i. LOD is defined as lowest concentration of DNA that can be detected in 95% of replicates
               ii. Upper and lower LOQ are highest and lowest concentrations of DNA that can be quantified with precision
            c. Lack of standardization between institutions
            a. Makes it possible for comparison of CMV PCRs across institutions
               i. Reported as international units (IU) per milliliter
            b. Not all institutions have adopted this standard

Prevention of CMV Infection and Disease Following Solid Organ Transplantation

I. Optimal prevention of CMV infection and disease after SOT can significantly improve outcomes
II. Prior to development of anti-CMV therapy
   a. CMV infection occurred in up to 80% of transplant recipients with a mortality rate of those who developed tissue invasive disease being about 80 to 90%
   b. Development of prophylactic strategies have reduced the incidence of CMV disease during the early posttransplantation period and minimized the effects of CMV disease
III. Prophylactic agents
   a. Ganciclovir (GCV) and valganciclovir (vGCV)
      i. Nucleoside analogues active against CMV and HSV
         1. GCV
            a. Developed in the mid-1980s
            b. Indicated for the treatment of CMV retinitis in immunocompromised patients and for the prevention of CMV in transplant recipients at risk for CMV disease
         2. vGCV
            a. Valyl ester prodrug of GCV
            b. Enhanced bioavailability and comparable efficacy to GCV
            c. Indicated for treatment of CMV retinitis in patients with AIDS, prevention of CMV in high-risk patients (D+/R-) undergoing kidney, heart, kidney/pancreas transplantation
ii. Mechanism of action (see Figure 2)

![Figure 2. Ganciclovir mechanism of action](image)

iii. Dosing
1. GCV 5 mg/kg IV daily, adjusted for renal dysfunction
2. vGCV 900 mg by mouth daily, adjusted for renal dysfunction
   a. Improved bioavailability with decreased pill burden

iv. Monitoring
1. Complete blood count (CBC): neutropenia > anemia > thrombocytopenia
2. Renal function
b. CMV immunoglobulin (CMV Ig)
   i. Immunoglobulin containing standardized amount of antibody to CMV
      1. Reduce incidence of serious CMV in those exposed to the virus
   ii. Indicated for prophylaxis of CMV disease after kidney, lung, liver, pancreas and heart transplantation
   iii. Limited data to support its use for prophylaxis
      1. Typically used only as an adjunct to antivirals

IV. Methods of prophylaxis
a. Universal prophylaxis
   i. Prophylactic antivirals initiated immediately posttransplantation
      1. Continued for three to twelve months
   ii. Prevention rates from 58% to 80%

b. Preemptive therapy
   i. Serial testing performed weekly or biweekly for the first few months posttransplantation
   ii. Regardless of symptoms, treatment doses of antivirals are administered with any early evidence of CMV replication
   iii. No widely acceptable viral load threshold to guide therapy due to lack of standardization of PCR results across centers

c. Hybrid approach
   i. Short term prophylaxis followed by preemptive therapy
   ii. Clinical utility and efficacy not validated

d. Advantages and disadvantages of prophylactic regimens (see Table 3)
   i. Optimal preventive regimens are undefined due to the lack of randomized, controlled trials

<table>
<thead>
<tr>
<th>Table 3. Comparison of Universal Prophylaxis and Preemptive Therapy</th>
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<td><strong>Universal Prophylaxis</strong></td>
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<td><strong>Efficacy</strong></td>
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<td><strong>Reduced indirect effects</strong></td>
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*Less optimal in high risk populations; potential failure of weekly surveillance with rapid viral replication

HSV=herpes simplex virus; PCR=polymerase chain reaction; VZV=varicella zoster virus
e. Consensus\textsuperscript{1-3} (see Table 4)
   i. Universal prophylaxis is the preferred strategy for high risk D+/R- transplant recipients
   ii. Preemptive therapy can be considered in moderate risk SOT patients
      1. R+
      2. Kidney, liver, and heart transplants

| Table 4. Consensus on the Use of Cytomegalovirus Prophylaxis Regimens* |
|-----------------------------|-----------|-----------|-----------|
| Duration                    | D+/R-     | R+        | D-/R-     |
| Liver, heart                | 3-6 months| 3 months  | --        |
| Kidney, pancreas            | 6 months  | 3 months  | --        |
| Lung                        | 6-12 months| ≥6 months| --        |
| Medication Regimen          |           |           |           |
| Kidney, pancreas            | vGCV or GCV| Acyclovir|           |
| Liver                       | vGCV or GCV| Acyclovir|           |
| Lung, heart                 | vGCV or GCV, ± CMV Ig| Acyclovir|

*See Appendix A for summary of major CMV prophylaxis trials
GCV= 5 mg/kg IV daily; vGCV= 900 mg by mouth daily

f. Late-onset disease after prophylaxis discontinuation
   i. Disease occurring after discontinuation of antiviral prophylaxis
      1. Typically within 3 to 6 months of antiviral discontinuation
   ii. Associated with higher rates of mortality and graft loss
   iii. About 30% of D+/R- kidney, heart, pancreas, and liver recipients develop late-onset CMV
        after completing three months of prophylaxis

Treatment of CMV Posttransplantation

I. Indications for treatment initiation\textsuperscript{1,2,CDVMPI}
   a. CMV viremia
      i. All patients with CMV disease
         ii. Asymptomatic viremia
            1. Patient and provider-specific

II. Treatment regimen\textsuperscript{25,26,13}
   a. Immunosuppressive dose reduction
   b. Antiviral medications

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Figure 3. Timeline of antiviral development
i. Foscarnet (FOS)
   1. Pyrophosphate analogue indicated for:
      a. Treatment of CMV retinitis in patients with acquired immunodeficiency syndrome (AIDS)
      b. Mucocutaneous acyclovir-resistant herpes simplex virus (HSV) infections in immunocompromised patients
   2. Directly inhibits viral DNA polymerase without prior phosphorylation (see Figure 4)
      a. Forms a complex with the pyrophosphate binding site of viral DNA polymerase
         i. Prevents the cleavage of pyrophosphate from deoxynucleotide triphosphates
   3. Limitations
      a. Nephrotoxicity
         i. Major dose-limiting side effect
         ii. Adequate hydration for prophylaxis recommended
            1. Prior to first infusion: 750 to 1000 mL NS or D5W
            2. Then, 750 to 1000 mL with each 90 to 120 mg/kg dose of FOS
      b. Electrolyte abnormalities
      c. Neurotoxicity
      d. Fever, nausea and vomiting, anemia, and diarrhea
   4. Use limited to patients who experience treatment failure with GCV or for those who have GCV contraindications due to neutropenia

![Figure 4. Pharmacologic mechanisms of antivirals used for CMV](image)

Figure 4. Pharmacologic mechanisms of antivirals used for CMV

ii. Cidofovir (CDV)
   1. Acyclic nucleoside phosphonate (ANP) derivative
      a. Must be phosphorylated via cellular kinases to diphosphoryl derivative to exert its antiviral activity (see Figure 4)
   2. Potent inhibitor and alternate substrate for viral DNA polymerase
   3. Indicated for treatment of CMV retinitis in patients with acquired immunodeficiency syndrome (AIDS)
   4. No data from randomized clinical trials to support its use in SOT recipients
   5. Advantageous pharmacokinetic profile allows once weekly dosing
6. Toxicity profile limits its use
   a. Nephrotoxicity
      i. Prophylaxis with fluids and probenecid recommended
         1. 1000 mL NS over 1 to 2 hours prior to CDV infusion
         2. Additional 1000 mL, infused over 1 to 3 hours, with start of CDV infusion or immediately following infusion, if tolerable
         3. Probenecid 2 g by mouth 3 hours prior to CDV
         4. Probenecid 1 g by mouth at 2 hours and 8 hours after completion of CDV infusion
   b. Neutropenia

III. Monitoring\(^1\)
   a. Response to treatment
      i. PCR monitoring on day of treatment initiation and weekly thereafter
   b. Adverse reactions

IV. Duration\(^1\)
   a. Continue treatment until one to two consecutive negative samples are obtained
      i. Minimum two weeks of treatment
      ii. Minimizes risk of disease recurrence and antiviral resistance

V. Secondary prophylaxis\(^1\)
   a. Treatment course followed by prophylactic dosing of antiviral medications to prevent recurrent disease
      i. Typically for one to three months

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**Figure 5. Risk factors for CMV disease recurrence\(^1\)**

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**CMV Antiviral Resistance**

I. Increasing or persistent viral load despite adequate antiviral therapy for greater than two weeks with confirmed resistance on genotypic and/or phenotypic testing\(^2\)

II. Prevalence and outcomes\(^1,7,20,22\)
   a. Estimates of antiviral resistance among SOT recipients varies greatly
      i. D+/R- recipients have highest incidence
         1. Rates of about 5% to 10% in D+/R- recipients being treated for CMV
      ii. Lung transplant recipients have been observed to experience higher rates of antiviral resistance than rates observed in other SOT recipients
         1. 17.6% of viremic lung transplant recipients versus 6.2% of viremic kidney recipients
   b. Clinical outcomes in SOT recipients after antiviral resistance development are poor
      i. Mortality rates 19% to 100%
III. Risk factors for antiviral resistance development\textsuperscript{1,2,7,23}
   a. Absence of preexisting CMV specific immunity prior to transplantation (D+/R-)
      i. Most consistently identified risk factor
   b. Prolonged or inadequate antiviral drug exposure
   c. Ongoing active viral replication
   d. High levels of immunosuppressive medications
   e. Lung transplant
   f. High peak viral load
      i. Greater than $10^5$ copies/mL in peripheral blood

IV. Mutations associated with antiviral resistance\textsuperscript{7,13,20,24}
   a. UL97 mutation (see Figure 6)
      i. Constitute greater than 95% of antiviral-resistant strains
   b. UL54 mutation (see Figure 6)
      i. UL54 gene encodes the viral DNA polymerase
      ii. Antiviral resistance depends of the site of the mutation of the viral DNA polymerase
         1. Can confer resistance to GCV, vGCV, FOS, and/or CDV
      iii. Isolated UL54 mutations uncommon
         1. Typically evolve after UL97 mutations
         2. Dual UL97/UL54 mutations present with high-grade GCV resistance ($IC_{50}\geq30\mu M$)
   iv. Mechanisms of resistance
      1. Reduced antiviral affinity
         a. Proposed mechanism for FOS resistance
      2. Reduced DNA chain incorporation
      3. Increased antiviral excision out of the DNA chain

\textbf{Figure 6. Mutations associated with antiviral resistance to cytomegalovirus}\textsuperscript{13}
V. Laboratory diagnosis of antiviral resistance\textsuperscript{7,13,20,24}

a. Rapid laboratory confirmation of antiviral resistance is important
   i. Increasing viral loads or disease progression may be due to host factors rather than antiviral resistance
      1. Empiric changes in antiviral treatment may therefore lead to unnecessary toxicity through exposure to other drug therapies
      2. Antiviral resistance should be confirmed before altering antiviral treatment regimens
         a. Except in life or sight-threatening disease

b. Phenotypic assay
   i. Reference standard for assessing antiviral susceptibility
      1. Labor intensive
      2. Four to six week turnaround time for results
      3. Rarely used in clinical practice
   ii. Determination of drug concentration required to inhibit 50\% or 90\% (IC\textsubscript{50} or IC\textsubscript{90}) of viral growth
      1. Specific sequence of clinical strain is transferred to a reference laboratory CMV strain
   iii. Proposed cutoffs for antiviral susceptibilities
      1. GCV IC\textsubscript{50}>6 to 12 \textmu M
      2. FOS IC\textsubscript{50}>300-500 \textmu M
      3. CDV IC\textsubscript{50} ≥2 \textmu M

c. Genotypic testing
   i. More commonly used in the clinical setting to test for CMV antiviral resistance
      1. Produces results in as quick as a few hours or up to three days
   ii. PCR amplification and sequencing of resistance loci from clinical specimens
      1. Compared to known resistant or wild-type strain to categorize mutation sensitivity to antivirals
      2. IC\textsubscript{50} ratio = IC\textsubscript{50} of mutant/IC\textsubscript{50} of wild type
         a. IC\textsubscript{50} ratio>3 is classified as resistance
         b. IC\textsubscript{50} ratio>5 is classified as major resistance
   iii. Disadvantage
      1. Resistance mutations cannot be distinguished from sequence polymorphisms without confirmation with phenotypic assays

VI. Cross-resistance between antiviral therapies\textsuperscript{20}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{ul97_mutation.png}
\caption{Cross-resistance observed among antiviral therapies\textsuperscript{20}}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{ul54_mutation.png}
\caption{Cross-resistance observed among antiviral therapies\textsuperscript{20}}
\end{figure}

\textbf{Treatment of GCV-Resistant CMV}

I. No controlled clinical trials to support the use of specific treatment regimens in cases where drug resistance is suspected or proven

II. Standardized approach to the treatment of antiviral-resistant CMV infection and disease is difficult
   a. Diversity of host factors affect clinical outcome in SOT recipients
b. Changes in therapy must consider potency, toxicity, and logistical complexity of the available alternative antiviral agents

III. Reduction of immunosuppressive therapy

a. Retrospective review of patient population included in the VICTOR trial

i. Significantly greater proportion of patients treated with dual versus triple immunosuppressive therapy eradicated CMV DNAemia by day 21 (71.3% vs. 52%)

ii. No effect on risk of recurrence

IV. Antiviral therapy

| Table 5. Comparison of Antiviral Agents Approved for Treatment of CMV |
|---------------|---------|---------|---------|
|               | GCV     | FOS     | CDV     |
| **Mechanism of action** | Inhibit viral DNA polymerase |
| **Indication** | -CMV retinitis | -CMV retinitis in AIDS | -CMV retinitis in AIDS |
| **Dose**<sup>b</sup> | 5 mg/kg IV twice daily | 90 mg/kg IV twice daily | 5 mg/kg IV once weekly |
| **Major adverse effects** | Neutropenia > anemia > thrombocytopenia | Nephrotoxicity, electrolyte abnormalities | Nephrotoxicity, neutropenia |
| **Mutations that confer resistance** | UL97 | UL54 | UL54 |

<sup>a</sup> Mucocutaneous acyclovir-resistant herpes simplex virus infections in immunocompromised patients

<sup>b</sup> Adjusted for renal function

a. Foscarnet

i. Case Reports<sup>28,29</sup>

| Table 6. Case Reports of Severe CMV Disease Treated with Foscarnet<sup>28,29</sup> |
|----------------|----------------|----------------|----------------|
|                | Patient 1      | Patient 2      | Patient 3      | Patient 4      |
| **Age (years)** | 59             | 64             | 40             | 52             |
| **Type of transplant** | Kidney       | Kidney         | Kidney         | Heart          |
| **Serology** | D?/R-               | D?/R-             | D?/R-            | D-/R- |
| **Induction** | --                | --              | --              | ATG            |
| **IS regimen** | CsA + CCS<sup>a</sup> | CsA + CCS<sup>a</sup> | CsA + CCS | TAC, AZA, CCS |
| **Rejection (day)** | 29             | 44             | 28, 4, 128 | --             |
| **Rejection treatment** | CCS           | CCS             | CCS         | --             |
| **Type of CMV disease** | PNA, Renal     | CNS?, PNA?     | PNA       | Gl?, Renal? |
| **CMV symptoms (day)** | 48             | 50             | <60 (not treated); 134 | 37 |
| **FOS initiation (day)** | 69             | 66             | 143           | 43             |
| **FOS dose (mg/kg/hr)** | 3.3           | 3.3           | 3.24           | ?             |
| **Duration of FOS (days)** | 5             | 5             | 8             | 15             |
| **Clinical improvement during treatment** | Y             | Y              | Y             | Y             |
| **Adverse events (SrCr<sub>ende</sub>-SrCr<sub>ende</sub>)** | ↑SrCr<sup>b,c</sup> (3.17-4.63) | -- (2.1-3.8) | -- (3.17-3.17) | ↑SrCr<sup>b,d</sup> (7.12-3.39) |

Alive + graft=patient alive with functioning graft; ATG=antithymocyte globulin; AZA=azathioprine; CCS=corticosteroid; CNS=encephalitis; CsA=cyclosporine; FOS=foscarnet; PNA=pneumonitis; SrCr<sub>ende</sub>=serum creatinine (mg/dL) at beginning and end of FOS therapy; TAC=tacrolimus

<sup>a</sup>Immunosuppression discontinued with symptom onset or initiation of FOS; <sup>b</sup>Patient also received gentamicin; <sup>c</sup>FOS discontinued due to nephrotoxicity; <sup>d</sup>Patient required hemodialysis even before initiation of FOS or gentamicin
c. Recent use of foscarnet and cidofovir
   i. Single center, retrospective analysis
   ii. 1549 SOT recipients who all received vGCV universal prophylaxis
   iii. 284 (18.3%) patients tested positive for CMV infection
       1. 20/56 recipients genotypically tested had resistance mutations
          a. 80% D+/R-
          b. Detected a median of 9 months posttransplantation

| Table 7. 20 Patients with Resistant Strains |
|-----------------|-----------------|-----------------|
| 16 UL97         | 1 UL54          | 3 UL97 and UL54 |
| 7 kidney        | 1 lung          | 3 lung          |
| 3 heart         |                 |                 |
| 3 lung          |                 |                 |
| 2 liver         |                 |                 |
| 1 kidney/pancreas|                |                 |

iv. Foscarnet and cidofovir therapy

![Diagram](image)

Figure 8. Patient population in Perez et al.30

v. Toxicity
   1. No significant changes in renal function were observed

vi. Take-home points
   1. FOS appears useful for the treatment of severe, symptomatic CMV disease
   2. Cases with known antiviral resistance were only presented in abstract form
      a. Many details unknown
   3. CDV appears useful for the treatment of CMV containing UL97 mutations
b. High-dose GCV
   i. Case series
      1. To assess the utility of high-dose GCV for the treatment of non-severe CMV replication in patients with GCV-resistant strains
      2. Clinical resistance
         a. Persistent viral load or symptom development after 2 weeks GCV or vGCV treatment
         b. Patients 1, 2, 3, and 5 had mutations conferring high grade resistance

| Table 8. Use of High-Dose GCV in Patients with Asymptomatic CMV Posttransplantation |
|----------------------------------|-----------------|----------------|----------------|----------------|----------------|----------------|
| Type of transplant               | Patient 1        | Patient 2       | Patient 3       | Patient 4       | Patient 5       | Patient 6       |
| Induction                        | Kidney           | Kidney          | Kidney          | Kidney-pancreas | Liver           | Kidney          |
| IS regimen                       | ATG              | --              | --              | --              | --              | --              |
| CMV serology                     | T/M/S            | T/M/S           | T/M/S           | T/M/S           | T/M/S           | T/M/S           |
| Prophylaxis                      | PT               | PT              | UP              | UP              | UP              | UP              |
| Symptomatic CMV replication      | N                | N               | N               | Y (Colitis)     | N               | N               |
| Mutation                         | UL97             | UL97            | UL97            | UL97            | UL97            | UL97           |
| Treatment regimen (duration in days) | Int GCV (12)     | Int GCV (7), Full GCV (21) | Int GCV (21) | Int GCV (28) | Int GCV (14), Full GCV (14), Int vGCV (14) | Full vGCV (56) |
| Dose limiting neutropenia        | Y (GCSF)         | N               | N               | N               | N               | N               |
| Outcome (time post-infection)    | Alive + graft (10 months) | Alive + graft (1 year) | Alive + graft (2 years) | Alive + graft (1 year) | Alive + graft (2 years) | Alive + graft (2 years) |

Alive + graft=patient alive with functioning graft; ATG=antithymocyte globulin; Full GCV=ganciclovir 10 mg/kg IV every 12 hours, adjusted for renal function; Full vGCV=valganciclovir 1800 mg by mouth twice daily, adjusted for renal function; GCSF=granulocyte colony-stimulating factor 30 x 10^6 for two doses; Int GCV=ganciclovir 7.5 mg/kg IV every 12 hours, adjusted for renal function; Int vGCV=valganciclovir 1350 mg by mouth twice daily, adjusted for renal function; IS=immunosuppressive; M=mycophenolate mofetil; N=no; PT=preemptive therapy; S=steroid; T=tacrolimus; UP=universal prophylaxis for 90 days with vGCV; Y=yes

^a UL54 mutation detected, but patient refused foscarnet, ^b High grade antiviral resistance

ii. Take-home points
   1. Non-severe, asymptomatic disease with UL97 mutations
   2. Dose-limiting neutropenia occurred in one of six patients
   3. Increasing doses of GCV were effective despite mutations conferring high-grade resistance
c. Combination therapy
   i. Synergy between GCV and FOS has been demonstrated in vitro\textsuperscript{32}
   ii. Other immunocompromised populations
      1. Addition of FOS to failing GCV monotherapy, or addition of GCV to failing FOS, has
         been shown to be superior to continuing monotherapy or switching to monotherapy
         with another medication\textsuperscript{33}
   iii. Case series\textsuperscript{34}
      1. Massachusetts General Hospital
         a. Oral GCV prophylaxis for 3 months posttransplantation
            i. D+/R-
            ii. R+ patients who receive antilymphocyte agents for induction or graft
               rejection
         b. CMV antigenemia assay monitored monthly
            i. Persistently positive antigenemia
               1. Treatment dose GCV IV and monthly CMV Ig
         c. CMV Disease
            i. Diagnosed 3 months to 2 years posttransplantation (median 5 months)

d. Treatment
   i. Combination therapy
      1. GCV 5 mg/kg IV daily
      2. FOS titrated to max of 125 mg/day
      3. CMV Ig
   e. Secondary prophylaxis
      i. Oral GCV and monthly CMV Ig for 3 months
   f. Adverse effects
      i. FOS-induced electrolyte abnormalities, specifically magnesium wasting
      ii. All patients had antigenemia levels of zero by 4 to 8 weeks
   g. No relapses observed after 12 to 36 month follow-up
   h. Take-home points
      i. Low-dose combination therapy of GCV and FOS can be beneficial in SOT
         recipients infected with GCV-resistant CMV
         1. Unknown which mutation was being treated
      ii. Magnesium wasting was the major adverse effect observed
1. Patients required 10 g to 24 g of magnesium supplementation daily
   iii. Regimen did not lead to increased antiviral resistance

V. Adjunct therapy\textsuperscript{1,35,36}
a. Immunosuppressive drugs with anti-CMV activity
   i. Leflunomide
      1. Prodrug indicated for the treatment of rheumatoid arthritis
      2. Immunosuppressive and antiviral properties
         a. Novel mechanism of action compared to currently used antivirals for CMV
            i. Inhibits B-cell and T-cell proliferation
            ii. Interferes with viral capsid assembly
      3. Dosing
         a. 100 mg/day by mouth for 3 days, followed by 20 mg/day
         b. Therapeutic monitoring
            i. Target range 50-80 mcg/mL
   4. Adverse reactions
      a. Diarrhea, anemia, hepatotoxicity
      b. Viral clearance delayed when compared to IV GCV
   5. Retrospective chart review\textsuperscript{36}
      a. 15 SOT recipients who received leflunomide after failure of other antivirals
         i. 13 D+/R-, 1 D-/R-, 1 unknown
         ii. 3 kidney, 1 pancreas, 5 kidney/pancreas, 2 heart, and 2 lung
      b. Patients receiving a calcineurin inhibitor, mycophenolate mofetil (MMF), and corticosteroid for immunosuppression
         i. Dose of MMF was typically reduced or removed from the regimen due to antirejection effects of leflunomide
         ii. 53% of patients achieved long-term suppression of CMV recurrences
      d. Testing form UL97 and UL54
         i. Via genotyping in 16 patients
    ii. Mammalian target of rapamycin (mTOR) inhibitor
       1. Both immunosuppressive and antiviral properties
       2. Some evidence that switching recipients’ immunosuppressive therapy to an mTOR inhibitor may lead to a lower incidence of CMV infection and disease

Future Options

I. Hexadecyloxypropyl cidofovir conjugate (CMX001)\textsuperscript{17}
   a. Orally bioavailable cidofovir derivative
      i. Not concentrated in the renal tubules, so less likely to cause nephrotoxicity
   b. Major adverse effect: diarrhea
   c. Cross-resistance with CDV expected
II. Letermovir (AIC246)\textsuperscript{1}
   a. Inhibits formation and release of infectious virus particles via targeting the UL56 viral terminase complex
   b. Currently undergoing phase II clinical trials
   c. No cross-resistance with current antivirals expected
III. Maribavir\textsuperscript{1,7}
   a. Oral UL97 inhibitor with good bioavailability and low toxicity
   b. Phase III trials in D+/R- liver SOT and hematopoietic stem cell transplant recipients
      i. No antiviral efficacy observed
      ii. Currently undergoing trials to investigate efficacy of maribavir at higher dose
   c. Resistance involves UL27 and UL97 genes
IV. Vaccine\textsuperscript{1}
   a. Currently under development, but none are available for clinical use
Summary and Recommendations

I. Summary
   a. CMV incidence has decreased dramatically with the implementation of ganciclovir prophylaxis
   b. When CMV does occur, it significantly impacts both patient and graft survival
   c. Resistance to ganciclovir is a growing problem among adult solid organ transplant recipients
   d. Inadequate literature to support treatment decisions when resistance is encountered
   e. Furthermore, lack of alternative antivirals, antiviral cross-resistance, and drug toxicity makes choosing an optimal treatment regimen difficult

II. Recommendations (see Figure 10)
   a. Selection of an alternative treatment regimen for GCV-resistant CMV is highly patient-specific
   b. Factors to consider
      i. Severity of disease, degree of immunosuppression, presence of concurrent organ rejection, viral load, mutations present, exposure and tolerability to previous antiviral medications
**Figure 10. Suggested treatment algorithm for ganciclovir-resistant cytomegalovirus**

**Suspected Resistance**

- Consider reducing immunosuppression
- Send for genotypic resistance testing

**Asymptomatic or Non-Severe CMV Disease**

High-dose GCV or Combination low-dose GCV + FOS

**Response?**

- Yes: Continue high-dose GCV or Combination therapy
- No: FOS

**Severe CMV Disease**

Life or sight-threatening disease

**Immediate change in antiviral therapy**

- FOS or CDV

CDV = cidofovir; CMV = cytomegalovirus; FOS = foscarnet; GCV = ganciclovir
References

27. Vistide [package insert]. Foster City, CA: Gilead Sciences, Inc.; September 2010
# Appendix

## Appendix A. Summary of Major Cytomegalovirus Prophylaxis Studies

<table>
<thead>
<tr>
<th>Study design</th>
<th>Paya et al. 38</th>
<th>IMPACT 39</th>
<th>Palmer et al. 19</th>
<th>Copeland et al. 40</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>372</td>
<td>326</td>
<td>136</td>
<td>38</td>
</tr>
<tr>
<td>Study design</td>
<td>P, R, DB, DD study</td>
<td>MC, DB, R, PC trial</td>
<td>P, MC, DB, PC, R trial</td>
<td>Follow up of Palmer et al. study</td>
</tr>
<tr>
<td>Serostatus</td>
<td>D+/R-</td>
<td>D+/R-</td>
<td>-D+/R- (33%)</td>
<td>-D+/R- (24%)</td>
</tr>
<tr>
<td></td>
<td>-D+/R+ (31%)</td>
<td>-D-/R+ (36%)</td>
<td></td>
<td>-R+ (76%)</td>
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<td>Type of transplant</td>
<td>-Heart</td>
<td>-Kidney</td>
<td>-Lung</td>
<td>-Lung</td>
</tr>
<tr>
<td></td>
<td>-Liver</td>
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<tr>
<td></td>
<td>-Kidney</td>
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<td></td>
<td>-Multiorgan</td>
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<tr>
<td>Intervention</td>
<td>vGCV 900 mg PO daily vs. GCV 1000 mg PO TID for prophylaxis</td>
<td>200 days vs. 100 days of vGCV 900 mg daily for CMV prophylaxis</td>
<td>vGCV 900 mg daily for 3 months vs. 12 months for prophylaxis</td>
<td>Mean follow up was 3.9 years</td>
</tr>
<tr>
<td>Outcome</td>
<td>-vGCV found to be as clinically effective and of comparable safety to GCV in D+/R- recipients</td>
<td>-Significantly fewer patients in 200 day group developed confirmed disease at 12 months posttransplantation without the cost of additional safety concerns -Incidence of allograft function, graft loss, and survival were not different between groups at 1 and 2 years</td>
<td>-Incidence of CMV was significantly greater in patients who received 3 months of prophylaxis versus 12 months</td>
<td>-Long-term prophylaxis prevents rather than simply delays onset of CMV disease without increasing GCV resistance or adverse events</td>
</tr>
</tbody>
</table>

CMV=cytomegalovirus; DB=double blind; DD=double dummy; D+/R+=donor/recipient serostatus; GCV=ganciclovir; MC=multicenter; N=number of patients; NS=not significant; P=prospective; PC=placebo controlled; PO=by mouth; R=randomized; TID=three times a day; vGCV=valganciclovir