Long-term success of transplant recipients requires an interdisciplinary approach that includes all healthcare providers involved in the management of these patients to prevent and treat CMV viremia. Therefore, this continuing medical education activity will target ID clinicians involved in the care of transplant recipients. These include ID physicians and pharmacists, nurses, microbiologists and allied healthcare providers.

**Learning Objectives**

Those attending the program will be able at its conclusion to:

- Recognize the burden of CMV and identify risk factors for CMV infection and disease
- Evaluate the benefits and risks of antiviral prophylaxis versus pre-emptive approaches in the prevention of CMV
- Assess the utility of advanced diagnostic monitoring tools to guide medical decision-making for patients with or at risk of CMV
- Describe the mechanisms of CMV resistance and assess the potential role of newer and emerging antiviral agents in overcoming resistance

---

**FACULTY**

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**Recognizing the Burden of CMV and Risk Factors for Infection**

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**Cytomegalovirus (CMV) Composition**

- Genetic composition
  - 2 unique regions of DNA (U\text{L} and U\text{S}), flanking terminal repeat regions (TR), and internal repeat region (IR)
  - Encodes ≥168 unique functional genes (exact number unknown)
  - Gene expression occurs in a temporal cascade (IE, early, and late)

---

**Effects of CMV Infection Post-Transplant**

- **CMV Viral Syndrome (SOT):**
  - Fever, malaise, myalgias
  - Leukopenia, thrombocytopenia, and other laboratory abnormalities

- **Tissue Invasive Disease (SOT/HSCT):**
  - Hepatitis
  - Pneumonitis
  - Colitis
  - Carditis
  - Nephritis
  - Pancreatitis
  - Retinitis

SOT, solid organ transplant; HSCT, hematopoietic stem cell transplant
The Burden of CMV

- Despite widespread use of preventive measures, CMV infection (viremia) and disease (symptoms) continues to be common in certain settings
- There has been:
  - Decrease in incidence of symptomatic disease
  - More commonly asymptomatic or mildly symptomatic viremia
  - Fewer cases of severe tissue invasive disease

However CMV Can Still Cause Life-Threatening Disease

Factors Influencing the Burden of CMV

- **Viral factors**
  - Replication dynamics
  - Immune evasion
  - Viral heterogeneity
  - Viral coinfections

- **Host factors**
  - CD4+, CD8+ T cell
  - NK cell, B cell
  - Exogenous immunosuppression
  - D/R immune status

Audience Question

Which of these patients is at highest risk of CMV disease?

1. D-/R+ HSCT recipient with acute graft-versus-host-disease
2. D+/R- lung transplant recipient
3. D+/R+ kidney transplant with steroid-resistant rejection treated with thymoglobulin
4. All of the above are at high risk

CMV PA THOGENESIS

INFLAMMATION

LATENT

CMV INFECTION

Reactivation of CMV

Host Immune Response to CMV

- Innate immunity
- Adaptive immunity
- Neutrophil
- Macrophage
- DC
- NK cell
- CD8+ T cell
- CD4+ T cell
- Cytotoxic CD8

INFLAMMATION

OTHER HERPESVIRIDAE

REJECTION

INFECTION
**CMV Infection to CMV Disease**

- Steroids
- CNI
- MMF/MPA
- SRL

**Risk Profile for CMV in SOT**

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Donor (D) / Recipient (R) Serologic Status (+/-)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>D+/R-</td>
</tr>
<tr>
<td>Intermediate*</td>
<td>D+/R-, D-R+</td>
</tr>
<tr>
<td>Low</td>
<td>D-R-</td>
</tr>
</tbody>
</table>

* D+/R+ generally at higher risk than D-R+ D-R-: leuko-depleted blood products or seronegative

**Risk of CMV in HSCT**

- Serostatus (in the US, ~60% population is CMV+)
  - D+/R-: 30% develop some degree of reactivation (although disease has been significantly reduced due to monitoring and preemptive therapy)
- High-dose steroids
- T cell depletion
- Acute and chronic GVHD
- Mismatched or unrelated donor
- Cord blood transplant (donors CMV negative)
- Alemtuzumab

**CMV PREVENTION: Prophylaxis**

- Prophylaxis
  - Antiviral therapy from the time of transplant to all patients or a subgroup of patients
  - E.g. 3–6 months of antiviral prophylaxis in all D+/R- transplant patients
  - Prophylaxis very successful in multiple clinical trials for CMV prevention

**What are the Major Problems with Prophylaxis?**

1. Drug toxicity – makes use of (val)ganciclovir as prophylaxis early post-HSCT unattractive
2. After discontinuation of prophylaxis – viremia and disease often develops
   - "Late-onset CMV disease"
   - May present with atypical symptoms (no fever – malaise, fatigue); diagnosis can be missed

**Viremia Common After Prophylaxis**

- GCV
- VGCV

---

CMV, cytomegalovirus; CNI, calcineurin inhibitors; MPA, mycophenolic acid; MMF, mycophenolate mofetil; SRL, sirolimus.
Extended Prophylaxis: Kidney Transplant Study

CMV Prevention: Preemptive Therapy

Can Either Oral or IV be Used for Preemptive Therapy?

Hybrid Strategy: Preemptive After Prophylaxis

The Burden of CMV: Indirect Effects

Role of Diagnostics in Monitoring CMV Infection and Treatment Response

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Head, Infectious Disease Sciences Program
Fred Hutchinson Cancer Research Center
Professor of Medicine, Division of Allergy and Infectious Diseases, Department of Medicine
University of Washington
Seattle, WA
Outline

- CMV viral load
  - Blood
    - Start of preemptive therapy
    - Monitoring treatment responses
  - BAL
    - Pulmonary shedding versus pneumonia

Preemptive Therapy

- Antiviral Drug
  - PCR, pp65 AG
  - pp67 mRNA

Bal, bronchoalveolar lavage

Preemptive Therapy PCR-based Risk-adapted Strategy

- Immunosuppression
- CMV reactivation
- Risk Groups

Viral Load Increases on Preemptive Therapy

- Up to 2 weeks not unusual
- Occurs with severe immunosuppression
- Antiviral resistance unusual

CMV Disease

Preemptive Era – Placebo Group in Randomized Trials

<table>
<thead>
<tr>
<th>Author</th>
<th>Journal</th>
<th>Year</th>
<th>N</th>
<th>Period</th>
<th>Incidence</th>
</tr>
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<tbody>
<tr>
<td>Marty et al.</td>
<td>Lancet ID</td>
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<td>227</td>
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<td>2.4%</td>
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<td>Marty et al.</td>
<td>NEJM</td>
<td>2014</td>
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<td>NEJM</td>
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<tr>
<td>Boeckh et al.</td>
<td>Ann Int Med</td>
<td>2014</td>
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<tr>
<td>Marty et al.</td>
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<td>149</td>
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<tr>
<td>Marty et al.</td>
<td>ASBMT</td>
<td>2017</td>
<td>170</td>
<td>Early</td>
<td>1.2%</td>
</tr>
</tbody>
</table>
CMV Pneumonia in HSCT Recipients

Diagnosis of CMV Pneumonia
Before 1988: Lung Biopsy

Shell Vial Cultures

Issues
Detection ≠ Disease
- PCR is highly sensitive – good NPV but poor PPV
- Asymptomatic shedding
- Pulmonary hemorrhage
- Distribution of viral load in the lung
- Radiographic presentation
- Need for appropriate controls

Cut-off value to distinguish pulmonary shedding from CMV pneumonia?

Case
- 57-year-old male, 112 days after HLA mismatched unrelated donor PBSC transplant for AML
- CMV R+D+, HSV+, VZV+
- Engraftment: day 14
- Acute GI GVHD, grade 3; current steroid dose: 0.6 mg/kg
- Two courses of ganciclovir/valganciclovir during the first 100 days, now presenting with shortness of breath, cough and bilateral interstitial infiltrates
- BAL results
  - CMV: shell vial cultures toxic; PCR: 910 IU/mL
  - Respiratory virus PCR panel negative
  - All other stains, Aspergillus GM and PCR, parafungal PCR, and cultures are negative
- Plasma CMV DNA PCR: 660 IU/mL

HLA, human leukocyte antigen; PBSC, peripheral blood stem cell; AML, acute myeloid leukemia; HSV, herpes simplex virus; VZV, varicella zoster virus; GM, galactomannan.

Audience Question
How do you interpret this result and what action do you take?
1. CMV pneumonia – treat with antivirals and IVIS/CMV Ig
2. CMV pneumonia – treat with antivirals only
3. CMV pulmonary shedding – treat with short-term antivirals
4. No treatment
Pulmonary Shedding of CMV


Study Methods

Cases: CMV pneumonia (N=132)
- BAL done 1988-2014
- SV, culture (+/- DFA, cytology) attempted
- Positive by at least one

Controls (N=139)
- SV and culture negative for CMV
- Asymptomatic HSCT recipients (N=21), normal chest x-ray around day 40
- Idiopathic pneumonia syndrome (IPS; no known pathogens) (N=18)
- Bacterial, fungal or viral (non-CMV) pneumonia (N=100)

Test by quantitative PCR
- Archived BAL
- Results in IU/mL (1 copy/mL = 1.2 IU/mL), plotted as log_{10}(IU/mL)

Quantitative CMV Load in BAL Fluid


Higher Viral Load in CMV Pneumonia Patients

No Impact of Pulmonary Hemorrhage


Impact of Radiographic Presentation?

Does viral load differ based on radiology?

Radiologic score
1 = Focal nodule
2 = Focal GGO
3 = Diffuse nodule
4 = Diffuse GGO

BAL CMV Load by Lung Imaging

No Difference in Viral Load

### ROC Curve: CMV Viral Load IU/mL

All CMV cases (N=132) and controls (N=118) (Asymptomatic patients excluded)

AUC = 0.915

Optimal cutoff point: 99.7 IU/mL

Sensitivity = 90.2%; Specificity = 80.5%

### Which Threshold is Most Predictive for CMV Pneumonia?

#### Prevalence of CMV pneumonia among patients who undergo bronchoscopy

**PPV**

**NPV**

#### Without antiviral agents at time of BAL

### Case - Interpretation

How do you interpret this result and what action do you take?

1. CMV pneumonia – treat with antivirals and IVIG/CMV-Ig
2. CMV pneumonia – treat with antivirals only
   
3. CMV pulmonary shedding – treat with short-term antivirals
4. No treatment

### Clinical Utility of Cytomegalovirus Viral Load in Bronchoalveolar Lavage in Lung Transplant Recipients

Roy F. Chemaly, Belinda Yen-Lieberman, Jeffrey Chapman, Amy Phily, S. Melnyk, Timothy A. Read, Tania Sancho, Deborah W. Shim, Emily M. Hurley, Malcolm DeCamp and Robin K. Avery


Threshold: 500,000 copies/mL
Take-Home Points

- CMV DNA-based preemptive therapy is effective in preventing CMV disease
- Increased viral load during the first two weeks of preemptive therapy is usually not due to drug resistance in drug-naive patients
- Quantitative DNA PCR of BAL fluid can differentiate between CMV pneumonia and asymptomatic shedding in HSCT recipients
- Pulmonary hemorrhage and copathogens, even with distinct radiographic presentation, did not seem to alter viral load
- Possible cut-off recommendations:
  - 500 IU/mL might provide improved PPV with acceptable NPV
  - Lower levels in highest risk patients
  - Shell vial testing may be helpful to assess patients with viral load <500 IU/mL
  - Threshold may differ between the HSCT and lung transplant setting

Utilizing Immune Monitoring Assays to Predict CMV Disease – SOT Focus

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Toronto, ON

Case

- 48-year-old man post DD liver transplant for HCV-related cirrhosis
- CMV D+/R-
- About to finish 3 months of antiviral prophylaxis

 Audience Question

What are the potential options to prevent late-onset CMV disease?

1. Do nothing and accept risk of late-onset CMV
2. Extend prophylaxis to 6 months
3. Check CMV PCR every week (hybrid strategy)
4. Check whether his T cells produce interferon-γ in response to CMV

Specific CMI Assays: Characterizing CMV-specific T Cells

Assays based on measurement of IFN-γ production by cells stimulated with CMV peptides, whole proteins, or CMV whole virus

ELISA-based Detection of IFN-γ (Quantiferon-CMV Assay)

- CD8+ T cell assay
  - Stimulated with a mixture of 23 peptides (pp65, IE1/2, gB, pp50)
  - ELISA gives IFN-γ value (IU/mL) – validated cut-off
- HLA-restricted so some HLA types not covered

Technical issues:
- 3 mL blood
- Results in 5-7 days
- Can be done at any center
- Sensitive to lymphopenia
ELISPOT

- Quantifies IFN-γ secreting cells (sfu per 100,000 cells)
- Total IFN-γ production by CD8+ or CD4+ T cells
- Threshold for positive result for CMV under study

Incubate 16–24h with CMV antigens

ELISPOT (T-SPOT®.CMV or T-Track® CMV)

Cytokine Flow Cytometry

- Provides highest resolution data for cytokines expressed by CD4+ and CD8+ T cells
- Primarily a research tool for CMV in many labs
- Limited by number of fluorochromes for each antibody
- No standardization

Summary of Clinical Studies of CMV Cell-mediated Immunity

- Numerous observational studies of CMI that have clinical endpoints (CMV disease or viremia)
- Include studies that have used ELISA, ELISPOT, or cytokine flow cytometry
- Majority of studies:
  - Measures IFN-γ release or enumerate IFN-γ+ T cells
  - Relatively small numbers
  - Heterogeneous population (mix of D+/R- and R+; various transplant types)
- Limited pediatric data

End of Prophylaxis CMI (D+/R- only)

Incidence of CMV Disease Based on CMI Assay Result

Potential Post-transplant Clinical Scenarios for CMI Use

<table>
<thead>
<tr>
<th>Clinical Scenario</th>
<th>Potential clinical management</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMV D+/- on primary prophylaxis</td>
<td>For negative assay, ongoing prophylaxis or frequent monitoring. For positive assay, no further prophylaxis or monitoring.</td>
</tr>
<tr>
<td>CMV R+ with other risk factors (e.g., lung transplant, ATG induction)</td>
<td>Post-therapy for acute rejection For positive assay, no further prophylaxis or monitoring.</td>
</tr>
<tr>
<td>Post-therapy for acute rejection</td>
<td>Recent completion of therapy for CMV disease (Prediction of relapse) For positive assay, continue to monitor.</td>
</tr>
<tr>
<td>Recent completion of therapy for CMV disease (Prediction of relapse)</td>
<td>Recent completion of therapy for CMV viremia (Prediction of relapse) For negative assay, start therapy. For positive assay, continue to monitor.</td>
</tr>
</tbody>
</table>

Utility of CMI in Another Clinical Scenario: Low-level Viremia

- 37 SOT patients enrolled at the time they had low-level CMV viremia (~1000 copies/mL)
- 78% spontaneously cleared whereas 22% progressed to require antivirals

**Utility of CMI in Another Clinical Scenario: Low-level Viremia**

**Utility of CMI in Another Clinical Scenario: Low-level Viremia**

**Utility of CMI in Another Clinical Scenario: Low-level Viremia**

**Utility of CMI in Another Clinical Scenario: Low-level Viremia**
Why CMI Assays are not yet in Routine Clinical Practice?

More interventional clinical studies are necessary!

- Several observational studies now show a link between T cell immunity and CMV viremia
- Studies in which a CMI assay is used in real time to make clinical decisions are ongoing:
  - Stopping prophylaxis early
  - Initiating antiviral treatment for low-level viremia
  - Withholding secondary prophylaxis from patients who finish CMV therapy and are CMV positive

More interventional clinical studies are necessary!

Utilizing Immune Monitoring Assays to Predict CMV Disease – HSCT Focus

Roy F. Chemaly, MD, MPH, FIDSA, FACP
Professor of Medicine
Director, Infection Control Section
Director of Clinical Virology
Department of ID/C/EH
UT MD Anderson Cancer Center
Houston, TX

How to Increase Specificity of Preemptive Therapy Approach?

- Combine monitoring of viral load with monitoring of CMV-specific T cell immunity
- This strategy allows withholding preemptive therapy in patients with low-to-moderate levels of CMV DNA, in presence of CMV-specific T cell responses
- However, protective T cell immunity thresholds need to be determined

Utility of the Enzyme-Linked Immunospot Interferon-γ Release Assay to Predict the Risk of CMV Infection in HCT Recipients

- Observational prospective study in 63 CMV-recipient positive HCT recipients
  - Low risk: MUD, haploidentical, CBT, GVHD, prednisone >1 mg/kg
  - Blood draws at specific time points from transplantation: H SCT—30—60—100 days
  - The primary objective: To assess the ability of an ELISPOT assay (T-SPOT.CMV) to predict CMV reactivation and/or disease in HCT recipients during the high-risk period

ELISPOT (T-SPOT®.CMV) Technology

Density gradient isolation of mononuclear cells
Quantitation of cells and adjustment of concentration
Incubation with specific antigens on ELISPOT microtiter plate

Clinical Characteristics and Outcomes at Day 100

<table>
<thead>
<tr>
<th>Trait</th>
<th>Median (IQR)</th>
<th>HCT—30</th>
<th>HCT—60</th>
<th>HCT—100</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (in years)</td>
<td>56 (21–73)</td>
<td>57 (21–69)</td>
<td>56 (24–73)</td>
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</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>37 (59)</td>
<td>14 (61)</td>
<td>23 (58)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>26 (41)</td>
<td>9 (39)</td>
<td>17 (43)</td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>White</td>
<td>49 (78)</td>
<td>17 (74)</td>
<td>32 (80)</td>
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<td>Hispanic</td>
<td>7 (11)</td>
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<td>5 (13)</td>
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<td>Asian</td>
<td>1 (2)</td>
<td>1 (4)</td>
<td>0</td>
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<tr>
<td>Type of Cancer</td>
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<td></td>
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<tr>
<td>Acute Leukemia</td>
<td>38 (60)</td>
<td>11 (48)</td>
<td>27 (68)</td>
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<tr>
<td>Chronic Leukemia</td>
<td>8 (13)</td>
<td>3 (13)</td>
<td>5 (14)</td>
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<tr>
<td>Myelodysplastic Syndrome</td>
<td>17 (27)</td>
<td>9 (39)</td>
<td>8 (20)</td>
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<tr>
<td>Type of Transplant</td>
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<td></td>
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<tr>
<td>Match Related Donor</td>
<td>23 (37)</td>
<td>5 (22)</td>
<td>18 (45)</td>
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<tr>
<td>Match Unrelated Donor</td>
<td>35 (56)</td>
<td>15 (65)</td>
<td>20 (50)</td>
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<tr>
<td>Cord</td>
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<td>3 (13)</td>
<td>2 (1)</td>
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<td>Corticosteroid use</td>
<td>19 (31)</td>
<td>5 (22)</td>
<td>14 (36)</td>
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<td>GVHD</td>
<td>12 (19)</td>
<td>4 (17)</td>
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<tr>
<td>HCT donor status</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>CMV +</td>
<td>41 (65)</td>
<td>13 (57)</td>
<td>28 (70)</td>
<td></td>
</tr>
<tr>
<td>CMV -</td>
<td>22 (35)</td>
<td>10 (43)</td>
<td>12 (30)</td>
<td></td>
</tr>
</tbody>
</table>

After the Proof of Concept

Definition of Events

**CMV Event:** The first episode of significant CMV reactivation, defined as the detection of CMV in blood via the antigenemia assay or the CMV PCR assay, after which anti-CMV therapy was initiated by the treating physician in accordance with institutional guidelines.

**CMV Disease:** The first episode of CMV disease, consisting of "end-organ disease" as defined by Per Ljungman et al.²

Results
Clinical Characteristics of 244 HCT Recipients

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>CMV Reactivation (n=59)</th>
<th>No CMV Reactivation (n=185)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
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<tr>
<td>Male</td>
<td>29 (49)</td>
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<td>Female</td>
<td>30 (51)</td>
<td>77 (42)</td>
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<tr>
<td>Race</td>
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<tr>
<td>White</td>
<td>40 (68)</td>
<td>138 (74)</td>
</tr>
<tr>
<td>African American</td>
<td>8 (14)</td>
<td>13 (7)</td>
</tr>
<tr>
<td>Asian</td>
<td>7 (12)</td>
<td>9 (5)</td>
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<td>Unknown/Other</td>
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<td>25 (14)</td>
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<td>Type of Transplant</td>
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</tr>
<tr>
<td>Match Related Donor</td>
<td>15 (25)</td>
<td>76 (41)</td>
</tr>
<tr>
<td>Match Unrelated Donor</td>
<td>31 (53)</td>
<td>79 (43)</td>
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<tr>
<td>Cord Blood</td>
<td>3 (5)</td>
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</tr>
<tr>
<td>Haploidentical</td>
<td>9 (15)</td>
<td>27 (14)</td>
</tr>
<tr>
<td>Unknown</td>
<td>1 (2)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>HCT donor status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CMV +</td>
<td>33 (56)</td>
<td>99 (54)</td>
</tr>
<tr>
<td>CMV -</td>
<td>24 (41)</td>
<td>72 (39)</td>
</tr>
<tr>
<td>Unknown</td>
<td>1 (2)</td>
<td>12 (7)</td>
</tr>
</tbody>
</table>

Scatterplot of IE1 Responses and Probability of CMV Events

KM Plot – Time from HCT to CMV Event

pp65 count >100 (high response)/≤100 (low response)

Cox Model for CMV Events Using Maximum pp65 as a Covariate, Retaining only Covariates with a p-value <0.15 via Stepwise Selection

- Endpoint:
  - Time to CMV Event
- The set of predictor variables were:
  - Maximum pp65 count >100
  - Recipient’s age
  - GVHD (Yes/No)
  - Transplant Type (4 categories: Cord Blood, Haploidentical, Matched or Mismatched unrelated donor, Unknown)
  - Receipt of systemic corticosteroids (Y/N)
  - Donor CMV sero-status (Positive/Negative)
  - Time to engraftment

Analysis of Maximum Likelihood Estimates

<table>
<thead>
<tr>
<th>Parameter</th>
<th>p-value</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Max pp65 count &gt;100</td>
<td>&lt;.001</td>
<td>0.081</td>
<td>0.042</td>
</tr>
<tr>
<td>Steroid Use</td>
<td>0.0056</td>
<td>0.124</td>
<td>1.790</td>
</tr>
</tbody>
</table>

Likelihood of CMV events

Summary

- IE1 spot counts ≥100 was a significant predictor of protection against CMV reactivation
- Trend towards lower mortality in patients with pp65 spot count ≥100
- After adjusting for different risk factors, pp65 spot count ≥100 was significantly associated with protection against CMV reactivation while the use of systemic steroids was significantly associated with CMV reactivation
Future Directions: CMV Immune Monitoring—Are We There Yet?

<table>
<thead>
<tr>
<th>Clinical Scenarios</th>
<th>Potential Clinical Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>As part of preemptive strategy</td>
<td>For negative assay, viral load monitoring and thresholds for initiating antiviral therapy</td>
</tr>
<tr>
<td>Post-therapy for GvHD</td>
<td>For negative assay, consider secondary prophylaxis, close monitoring; for positive assay, no further therapy</td>
</tr>
<tr>
<td>Recent completion of therapy for CMV disease or viremia (Prediction of recurrence of viremia)</td>
<td>For negative assay, consider or add secondary prophylaxis or preemptive therapy; for positive assay, no further therapy</td>
</tr>
<tr>
<td>Risk stratification in patients pre-transplantation</td>
<td>For positive assay, assume true positive CMV status</td>
</tr>
</tbody>
</table>

Prevention of CMV: Latest Approaches in Prophylaxis and Pre-emptive Strategies

Roy F. Chemaly, MD, MPH, FIDSA, FACP
Professor of Medicine
Director, Infection Control Section
Division of Clinical Virology
Department of ID/IC/EH
UT MD Anderson Cancer Center
Houston, TX

New Anti-CMV Approaches in Development

CMV Prophylaxis in HCT Recipients (n=230)

Brincidofovir Phase II Study Design

<table>
<thead>
<tr>
<th>Study Group</th>
<th>No. of Patients with CMV events (%)</th>
<th>Difference (%)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>10 (17)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>CMX001 40 mg weekly</td>
<td>13 (22)</td>
<td>-0.23</td>
<td>0.23</td>
</tr>
<tr>
<td>CMX001 100 mg weekly</td>
<td>16 (27)</td>
<td>-0.32</td>
<td>0.22</td>
</tr>
<tr>
<td>CMX001 200 mg weekly</td>
<td>10 (18)</td>
<td>-0.33</td>
<td>0.53</td>
</tr>
<tr>
<td>CMX001 200 mg twice weekly</td>
<td>12 (21)</td>
<td>-0.24</td>
<td>0.24</td>
</tr>
<tr>
<td>CMX001 100 mg twice weekly</td>
<td>5 (9)</td>
<td>-0.02</td>
<td>0.02</td>
</tr>
</tbody>
</table>

No evidence of increased myelosuppression or nephrotoxicity!

Primary Efficacy Endpoint in the Brincidofovir Groups as Compared with Placebo

<table>
<thead>
<tr>
<th>Study Group</th>
<th>Adverse Events (%)</th>
<th>Diarrhea (%)</th>
<th>Phlebitis (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>7</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>CMX001 40 mg weekly</td>
<td>4</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>CMX001 100 mg weekly</td>
<td>7</td>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td>CMX001 200 mg weekly</td>
<td>5</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>CMX001 200 mg twice weekly</td>
<td>66</td>
<td>80</td>
<td>80</td>
</tr>
<tr>
<td>CMX001 100 mg twice weekly</td>
<td>30</td>
<td>10</td>
<td>8</td>
</tr>
</tbody>
</table>

No evidence of increased myelosuppression or nephrotoxicity!
Brincidofovir vs Placebo in HCT Recipients Phase III

First Significant Observation

GVHD events on BCV were predominantly the gut, not skin, suggesting the diagnosis was driven by diarrhea.

GVHD events on BCV were predominantly the gut, not skin, suggesting the diagnosis was driven by diarrhea.

GVHD Stage

<table>
<thead>
<tr>
<th>N (%)</th>
<th>Brincidofovir (n=303)</th>
<th>Placebo (n=149)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1</td>
<td>49 (16.2)</td>
<td>3 (1.6)</td>
</tr>
<tr>
<td>Stage 2</td>
<td>42 (13.9)</td>
<td>14 (4.6)</td>
</tr>
<tr>
<td>Stage 3</td>
<td>22 (7.3)</td>
<td>7 (2.3)</td>
</tr>
<tr>
<td>Stage 4</td>
<td>0</td>
<td>6 (2.0)</td>
</tr>
</tbody>
</table>

The median cumulative exposure to corticosteroids was 8-fold higher in subjects on the BCV arm than those on placebo.

What’s Next for Brincidofovir? Intravenous Formulation

• Bypassing the gut appears to avoid local irritation and decrease incidence of diarrhea.

• Preliminary data from 28-day preclinical study show that IV BCV has a significantly lower risk of GI effects.
  — Maintained body weight during dosing.
  — No evidence of injury in preliminary review of the GI tract.

CMV Prophylaxis in HCT Recipients

Letermovir Phase II Study Design (n=131)

Screening

- Engraftment, no detectable CMV DNA and able to swallow.

Study Drug Administration (Weeks 12)

- Study Drug
- Preemptive Rx

Follow-up

- Day +10
- 30 days post transplantation or engraftment.

Primary endpoint: Incidence and time to onset of all-cause failure of prophylaxis against CMV infection during the 12 weeks of study drug.


**Letermovir Phase II Dose Escalation Efficacy Data**

<table>
<thead>
<tr>
<th>Study Group</th>
<th>Letermovir 60 mg</th>
<th>Letermovir 120 mg</th>
<th>Letermovir 240 mg</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>AHR failure %</td>
<td>48</td>
<td>21</td>
<td>12</td>
<td>61</td>
</tr>
<tr>
<td>Virologic failure %</td>
<td>17</td>
<td>8</td>
<td>0</td>
<td>29</td>
</tr>
<tr>
<td>Letermovir vs. placebo (p value)</td>
<td>0.03</td>
<td>0.005</td>
<td>0.003</td>
<td>-</td>
</tr>
</tbody>
</table>

**Chemaly RF, et al.**


**Letermovir vs Placebo in HSCT Recipients Phase III**

**Safety Outcome During Treatment Phase, %**

<table>
<thead>
<tr>
<th>Safety Outcome During Treatment Phase, %</th>
<th>Letermovir</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>37.0</td>
<td>50.0</td>
</tr>
<tr>
<td>Drug-related AE</td>
<td>14.0</td>
<td>12.0</td>
</tr>
<tr>
<td>Serious AE</td>
<td>44.0</td>
<td>46.0</td>
</tr>
<tr>
<td>• Infection</td>
<td>20.0</td>
<td>18.0</td>
</tr>
<tr>
<td>• GVHD</td>
<td>9.0</td>
<td>10.0</td>
</tr>
<tr>
<td>• Relapse of AML</td>
<td>4.0</td>
<td>4.7</td>
</tr>
<tr>
<td>• Acute kidney injury</td>
<td>1.3</td>
<td>4.7</td>
</tr>
<tr>
<td>• Diarrhea</td>
<td>0.5</td>
<td>2.6</td>
</tr>
<tr>
<td>• Atrial arrhythmia</td>
<td>0.5</td>
<td>0.0</td>
</tr>
<tr>
<td>Discontinuation due to AE</td>
<td>15.3</td>
<td>51.6</td>
</tr>
<tr>
<td>• CMV treatment</td>
<td>2.9</td>
<td>32.5</td>
</tr>
<tr>
<td>• Other</td>
<td>13.3</td>
<td>12.2</td>
</tr>
</tbody>
</table>

GVHD was the most common AE of any severity (39% in both groups)

- Diarrhea, nausea, fever, and rash also occurred in <20% of pts in both groups with similar frequency

**Ljungman P, et al.**

Hematological Analyses

- No evidence of bone marrow suppression
- Hematological lab parameters similar between letermovir and placebo
- >60% of subjects had not engrafted at baseline:
  - Incidence of engraftment similar between letermovir (95%) and placebo (91%)
  - Median time to engraftment similar between letermovir (19 days) and placebo (18 days)

CMV Prophylaxis in HSCT Recipients
Maribavir Phase II Data

<table>
<thead>
<tr>
<th>Treatment</th>
<th>100 mg bid (N=28)</th>
<th>400 mg qid (N=30)</th>
<th>400 mg bid (N=27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>57% 15% 0.001</td>
<td>57% 30% 0.031</td>
<td>57% 15% 0.001</td>
</tr>
<tr>
<td>Maribavir</td>
<td>11% 0% 0.000</td>
<td>11% 0% 0.000</td>
<td>11% 0% 0.000</td>
</tr>
</tbody>
</table>

CMV Prophylaxis in HSCT Recipients
Maribavir Phase III

Maribavir vs Placebo in HSCT Recipients Phase III

AEs Reported in ≥10% of Patients (ITT, Safety Population)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Placebo (n=223)</th>
<th>Maribavir (n=451)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with ≥1 adverse event</td>
<td>213 (96%)</td>
<td>440 (98%)</td>
</tr>
<tr>
<td>Acute graft-versus-host disease</td>
<td>74 (32%)</td>
<td>164 (36%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>65 (19%)</td>
<td>93 (21%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>39 (18%)</td>
<td>72 (16%)</td>
</tr>
<tr>
<td>Headache</td>
<td>36 (16%)</td>
<td>71 (16%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>20 (9%)</td>
<td>44 (10%)</td>
</tr>
<tr>
<td>Weight decrease</td>
<td>17 (8%)</td>
<td>63 (14%)</td>
</tr>
<tr>
<td>Rash</td>
<td>11 (5%)</td>
<td>60 (13%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>10 (5%)</td>
<td>52 (12%)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>10 (5%)</td>
<td>46 (10%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>5 (3%)</td>
<td>43 (10%)</td>
</tr>
<tr>
<td>Anemia</td>
<td>5 (3%)</td>
<td>42 (9%)</td>
</tr>
<tr>
<td>Perforated ulcers</td>
<td>5 (3%)</td>
<td>38 (9%)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>5 (3%)</td>
<td>24 (6%)</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>4 (2%)</td>
<td>32 (7%)</td>
</tr>
<tr>
<td>Weight increase</td>
<td>4 (2%)</td>
<td>14 (3%)</td>
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Maribavir vs Placebo in HSCT Recipients Phase III

AEs Reported in ≥10% of Patients (ITT, Safety Population)

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</tr>
<tr>
<td>Weight increase</td>
<td>4 (2%)</td>
<td>14 (3%)</td>
</tr>
</tbody>
</table>
Conclusions

• Ganciclovir and valganciclovir remain first-line agents for prophylaxis/preemptive treatment of CMV reactivation, but are associated with side effects (especially myelosuppression and renal toxicity)

• Novel anti-viral agents with different MOA have the potential to render prophylactic therapy more feasible, though it remains to be determined whether prophylaxis will impact transplant outcomes associated with CMV seropositivity

Mechanisms of CMV Resistance and Emerging Tools to Overcome It

Michael J. Boeckh, MD, PhD
Member, Vaccine and Infectious Disease & Clinical Research Divisions
Head, Infectious Disease Sciences Program
Fred Hutchinson Cancer Research Center
Professor of Medicine, Division of Allergy and Infectious Diseases, Department of Medicine
University of Washington
Seattle, WA

Antiviral Targets of Approved CMV Drugs: DNA Polymerase

Genotypic Basis of CMV Resistance

Resistant CMV: Not Everyone is at Risk

Viral Load Patterns with Preemptive Therapy
Who is at Risk for Increasing Viral Load?

Factors Associated with GCV-resistant CMV

<table>
<thead>
<tr>
<th></th>
<th>Cases (n=37)</th>
<th>Controls (n=109)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>28 (75.7)</td>
<td>63 (57.8)</td>
<td>0.052</td>
</tr>
<tr>
<td>Induction Immunosuppression*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>31 (86.1)</td>
<td>81 (74.3)</td>
<td>0.09</td>
</tr>
<tr>
<td>No</td>
<td>5 (13.9)</td>
<td>13 (13.8)</td>
<td></td>
</tr>
<tr>
<td>Induction Immunosuppression Type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-lymphocyte antibody</td>
<td>17 (46.7)</td>
<td>30 (44.2)</td>
<td>0.45</td>
</tr>
<tr>
<td>IL-2 receptor antagonist</td>
<td>14 (42.4)</td>
<td>43 (59.3)</td>
<td></td>
</tr>
<tr>
<td>Other (n=16)</td>
<td>166 (147-268)</td>
<td>143 (112-230)</td>
<td>0.053</td>
</tr>
<tr>
<td>Days to CMV diagnosis post transplant, median (range)</td>
<td>103 (31-218)</td>
<td>81 (15-198)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Ganciclovir/Valganciclovir Exposure Prior to Drug-resistant CMV

<table>
<thead>
<tr>
<th>Days of ganciclovir/valganclovir received prior to development of ganciclovir-resistant CMV in patients by type of organ transplanted</th>
<th>Organ transplanted</th>
<th>Days of ganciclovir/valganclovir received, median (range)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All organs (n=37)</td>
<td>153 (30-284)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung (n=17)</td>
<td>121 (30-260)</td>
<td></td>
<td>p&lt;0.02</td>
</tr>
<tr>
<td>Non-lung (n=20)</td>
<td>160 (30-284)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Outcomes Associated with GCV-resistant CMV

Case

- 51-year-old male with history of AML, s/p unrelated allogeneic myeloablative PBSCT
- Serostatus: CMV D+R+, HSV+, VZV+
- Post-transplant complications
  - Acute GVHD (skin, GI)
  - Organizing pneumonia 12 months after HSCT
- Recurrent CMV reactivation episodes
  - Day 38: 8 weeks of ganciclovir
  - Day 117: increasing levels (max 2500 IU/mL) on ganciclovir, UL97 positive for A594V
    - Switch to foscarnet
    - Seizure due to electrolyte abnormalities
    - Continued foscarnet with close monitoring resulting in viral load decline to 0
    - One additional episode treated successfully with valganciclovir

AML, acute myeloid leukemia; PBSCT, peripheral blood stem cell transplantation; HSV, herpes simplex virus; VSV, varicella zoster virus
Case - continued

- Now (22 mo after HSCT) he presents again with increasing viral load on maintenance VGCV.
  - Current episode:
    - Viral load: 1100 IU/mL, 900 mg VGCV twice daily
    - Initial response (below level of detection), switch to maintenance: 900 mg/day
    - UL97 mutation still present: A594V
    - Now 1100 IU/mL
  - Other relevant information:
    - Creatinine clearance: 67 mg/min/m²
    - WBC: 4100 per mm³, ANC: 1400 per mm³
    - Electrolytes within normal limits
    - Weight: 94 kg (BMI: 34 kg/m²)
  - Physical exam: unremarkable
  - Social history:
    - Lives in a small town
    - Presently no line access

VGCV, valganciclovir; ANC, absolute neutrophil count

Audience Question

What would you do next?

1. Continue current dose of valganciclovir
2. Double the dose of valganciclovir (re-induction)
3. Place a line and start IV ganciclovir
4. Place a line and start foscarnet

Question: What would you do next?

1. Continue current dose of valganciclovir – increase indicates lack of effectiveness (low levels, fixed dosing, high weight)
2. Double the dose of valganciclovir (re-induction) – viral load was still relatively low
3. Place a line and start IV ganciclovir - logistically difficult
4. Place a line and start foscarnet – logistical issues, prior toxicity

Case - continued

After one week, viral load increased further to 1800 IU/mL on valganciclovir 900 mg twice daily

Audience Question

What would you do next?

1. Increase the dose of valganciclovir to 1350 mg twice daily, provide G-CSF as needed
2. Keep current dose of valganciclovir and add leflunomide
3. Place a line/access and start IV ganciclovir at 7.5 mg/kg plus preemptive G-CSF
4. Place a line/access and start foscarnet

Question: What would you do next?

1. Increase the dose of valganciclovir to 1350 mg twice daily, provide G-CSF as needed – theoretically an option but no data or experience with this dose
2. Keep current dose of valganciclovir and add leflunomide – limited data, concern that it would be less effective and potentially toxic (remote outpatient setting)
3. Place a line/access and start IV ganciclovir at 7.5 mg/kg plus preemptive G-CSF
4. Place a line/access and start foscarnet – due to prior experience there was great reluctance to do this
**UL97 Mutations and Level of Resistance**

- Low level of resistance
- Intermediate level of resistance
- High level of resistance

**High-Dose Ganciclovir**

- Emerging experience
  - Adjusted max dose >40 mg/kg/day
- 7.5–10 mg/kg twice daily
  - Adjusted for renal function
  - Testing drug levels
- Valganciclovir
  - Fixed dose
  - Leuc drug levels – weight
  - No clinical data on higher doses
- Toxicity
  - G-CSF: preemptive vs. salvage
  - HIV experience
  - Fred Hutch experience

**Preemptive G-CSF**

- Scale-up prevents acute marrow aplasia and deaths
- Failure rates in patients receiving ganciclovir for cytomegalovirus infection

**Intervention**

- **Existing drugs**
  - Maribavir
  - Letermovir
  - Brincidofovir
  - T cell therapies
  - Monoclonal antibodies

**How I Treat**

**Maribavir**

- Potent member of a new class of drugs, the benzimidazole ribosides
- Inhibits the CMV UL97 kinase by competitively inhibiting the binding of ATP to the kinase ATP-binding site
- Active against wild-type and ganciclovir-resistant CMV strains
- 3- to 20-fold more potent than ganciclovir and cidofovir, and at least 100-fold more potent than foscarnet1,2

Past Studies with Maribavir

- Phase 3 trials for CMV prevention
  - Maribavir prophylactically administered at 100 mg BID for up to 12 weeks post-HCT
  - Failed to reduce the incidence of CMV disease within 6 months (Study 1263-300)

Two Phase 2 studies were conducted to assess the safety, tolerability, and anti-CMV activity of maribavir for treatment of CMV infections:
- In transplant recipients with resistant/refractory CMV infection or disease and with wild-type CMV infections without disease
- 3 dose strengths: 400, 800, or 1200 mg BID
- Both studies demonstrated favorable anti-CMV activity, the drug was well-tolerated, and there were no safety concerns at all doses evaluated

Maribavir: High Dose Phase II Results

- Most TEAEs were mild–moderate in severity.
- Gastrointestinal AEs: MBV (20–23%) versus VGC (10–15%)
- Dysgeusia: MBV (40%) versus VGC (3%), no apparent dose effect
- Neutropenia (ANC <1000/mm³): MBV (5%) versus VGC (18%)

<table>
<thead>
<tr>
<th>Maribavir (MBV)</th>
<th>VGC</th>
</tr>
</thead>
<tbody>
<tr>
<td>MBV dose</td>
<td>All MBV doses, N=120</td>
</tr>
<tr>
<td>400 mg BID</td>
<td>73/117 (63); 53, 70</td>
</tr>
<tr>
<td>800 mg BID</td>
<td>60/119 (50); 40, 72</td>
</tr>
<tr>
<td>1200 mg BID</td>
<td>OR 1.42; 95% CI 0.62, 3.24; P=0.41</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
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<tr>
<td>800 mg BID</td>
<td>60/119 (50); 40, 72</td>
</tr>
<tr>
<td>1200 mg BID</td>
<td>OR 2.12; 95% CI 0.91, 4.96; P=0.08</td>
</tr>
</tbody>
</table>

Maribavir: High Dose Phase II Results

- Most TEAEs were mild–moderate in severity.
- Gastrointestinal AEs: MBV (20–23%) versus VGC (10–15%)
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<tr>
<td>1200 mg BID</td>
<td>OR 1.42; 95% CI 0.62, 3.24; P=0.41</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>MBV dose</th>
<th>All MBV doses, N=120</th>
</tr>
</thead>
<tbody>
<tr>
<td>400 mg BID</td>
<td>73/117 (63); 53, 70</td>
</tr>
<tr>
<td>800 mg BID</td>
<td>60/119 (50); 40, 72</td>
</tr>
<tr>
<td>1200 mg BID</td>
<td>OR 2.12; 95% CI 0.91, 4.96; P=0.08</td>
</tr>
</tbody>
</table>

Maribavir Phase III

A Phase 3, Multicenter, Randomized, Open-label, Active-controlled Study to Assess the Efficacy and Safety of Maribavir Treatment Compared to Investigator-assigned Treatment in Transplant Recipients With Cytomegalovirus (CMV) Infections That Are Refractory or Resistant to Treatment With Ganciclovir, Valganciclovir, Foscarnet, or Cidofovir
Clinicaltrials.gov NCT02931539
Status: enrolling

A Phase 3, Multicenter, Randomized, Double-blind, Double-dummy, Active-controlled Study to Assess the Efficacy and Safety of Maribavir Compared to Valganciclovir for the Treatment of Cytomegalovirus (CMV) Infection in Hematopoietic Stem Cell Transplant Recipients
Clinicaltrials.gov NCT02931539
Status: enrolling

Potential Role of Other Emerging Antivirals

- Letermovir
  - Highly specific against CMV
  - Phase III for prophylaxis completed
  - Limited data on treatment

- Brincidofovir
  - Broad-spectrum activity, including CMV and ADV
  - Phase III completed – GI toxicity
  - Development continues for ADV
  - IV preparation being developed

Cellular Therapy

- Cellular Therapy

CMV Resistance: Take-Home Points

- UL97 can occur after prolonged ganciclovir exposure
- The level of susceptibility of different mutations matters
- Fixed-dose regimens may not work in all treatment situations
  - Weight
  - Renal function close to the adjustment threshold
- Testing of ganciclovir levels – limited data, availability
- High-dose ganciclovir may overcome low- and intermediate-level resistance
- Preemptive G-CSF may be an option to delay the development of neutropenia
- New drugs and immunotherapies are presently being evaluated in clinical trials