Current and Future Treatment of Cytomegalovirus Infection

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Disclosures

• Robin Avery MD has been a co-investigator on multicenter CMV-related studies funded by Shire, Viropharma, Merck, Astellas, Chimerix, and Oxford Immunotec.

• No personal financial remuneration from any pharmaceutical company.

• Off-label use of valganciclovir, leflunomide, IVIg, CMV Ig; and investigational maribavir, brincidofovir, and letermovir will be discussed in this presentation.
Timetable of Infection Following Organ Transplantation
(Fishman and Rubin, NEJM 1998; 338:1741-51)
CMV – Still a major issue in transplantation

• Despite advances in prevention strategies, CMV has not been eliminated
• A variety of complex CMV syndromes still occur, including antiviral-resistant CMV, and refractory CMV without genotypic resistance
• These are some of the sickest patients and some of the most challenging situations that transplant clinicians see
Abbreviations

- CMV – cytomegalovirus
- SOT – solid organ transplant
- HSCT – hematopoietic stem cell transplant
- D+ (seropositive donor); D- (seronegative donor)
- R+ (seropositive recipient); R- (seronegative recipient)
- GCV – ganciclovir; VGCV - valganciclovir
- FOS – foscarnet; CDV – cidofovir
- IVIg – intravenous immune globulin
Background

• Historically, CMV has been one of the most important transplant-related infections in both SOT and HSCT recipients
• Donors and recipients are screened for CMV serology (CMV IgG) prior to transplant; serostatus is an important risk factor
• CMV reactivation can occur from the recipient’s own strain, or a new strain can be acquired from the donor
Background

• D+/R- serostatus is the highest risk group in SOT and the most likely to develop high viral loads, tissue-invasive CMV disease, recurrences, and resistance.

• HSCT is a different situation because the recipient reconstitutes their immune system from the donor. HSCT R+ with CMV negative donors have more difficulty controlling CMV.
CMV Clinical Presentations

• Asymptomatic viremia
• “CMV Syndrome” (defined only for SOT): flulike syndrome with leukopenia, thrombocytopenia, slight LFT elevations
CMV Clinical Presentations

• Magnitude of CMV viral load often correlates with severity of illness (though not always)
• High viral load: risk for tissue-invasive disease, recurrences, resistance
• High viral load and highly symptomatic disease associated with long and complex courses, multiorgan dysfunction, debilitation
Prevention Strategies

• **Prophylaxis**: Administration of an antiviral (usually valganciclovir) to all transplant recipients at risk for CMV

• **Pre-Emptive Therapy**: Administration of an antiviral (usually valganciclovir) only to those who develop CMV viremia on serial monitoring of a sensitive test (CMV qPCR)
Prevention Strategies

• Prophylaxis generally used in SOT (3 mos for R+, 6 mos for D+/R-)
• Pre-emptive therapy generally used in HSCT (e.g. weekly CMV PCR to Day 100)
• In HSCT, prophylaxis has been avoided due to neutropenia risk from ganciclovir and valganciclovir
Treatment of CMV

• Historically was IV ganciclovir
• Oral ganciclovir was poorly bioavailable
• Valganciclovir is now used for treatment of viremia with low-to-moderate viral load and/or mild to moderate symptoms
• IV ganciclovir used for severe disease, high viral load, valganciclovir failure, or GI absorption issues
Treatment of CMV: Currently Available Drugs

- Ganciclovir and valganciclovir
- Foscarnet
- Cidofovir
- Occasionally, adjunctive therapy with IVIg or CMV hyperimmune globulin (CMVIg), especially in HSCT with CMV pneumonitis
Valganciclovir
Valganciclovir

• Oral agent with higher bioavailability than oral GCV; levels closer to those of IV GCV
• Ease of administration allows for possibility of lengthy courses and long-term viral suppression
• Secondary prophylaxis after a 1st CMV episode
• Disadvantages include cost, toxicity (neutropenia, thrombocytopenia), need for close monitoring, teratogenicity
• Neutropenia - a huge problem in real-world clinical practice
VICTOR Study

- The VICTOR study was a multinational, randomized, non-inferiority trial of 321 SOT pts with CMV
- Included tissue-invasive disease (40%)
- About ¾ were kidney recipients; few lung recipients
- Randomized to IV GCV vs. oral valganciclovir therapy (21d), followed by oral valganciclovir “tail” 28d
VICTOR Study

• Results: Valganciclovir was noninferior; similar rates of virologic clearance at 21 and 49 days
• Followup study did not show excess of GCV resistance nor recurrences, nor allograft dysfunction in either group
• Keep in mind that the most severely ill patients were not included and this was predominantly kidney recipients
VICTOR Study
So what’s the problem?

• Valganciclovir did not eradicate viremia in all patients in the VICTOR study (45-48% at 21 days, 67-70% at 49 days)

• Baseline viral load predictive of eradication

• Leukopenia occurred in 11-12% in the VICTOR study, but it is higher in actual usage

• Recurrences occur, and resistance becomes more likely over time
Antiviral-Resistant CMV

• UL97 mutations most common: GCV resistance (triphosphorylation by viral thymidine kinase)
• UL54 mutations (DNA polymerase) less common and may confer GCV, FOS, or CDV resistance
• Risk factors: D+/R-, recurrences, intensified immunosuppression
• Very important: Subtherapeutic concentrations of GCV/VGCV when the viral load is rapidly rising
Antiviral Resistance Sites
(Lurain NS, Chou S, Clin Microbiol Rev 2010; 23:689-712)
Traditional Therapy for GCV-Resistant/Refractory CMV

- Foscarnet – nephrotoxicity, electrolytes, GU ulcers
- Cidofovir – nephrotoxicity, ocular toxicity (uveitis, loss of intraocular pressure)
- Combination GCV/FOS (Mylonakis, Clin Infect Dis 2002)
- High-dose IV ganciclovir
- CMV Ig as adjunct to therapy
- Reduction of immunosuppression and/or switch to mTOR-based immunosuppression
GCV-R CMV in Lung Transplant, Foscarnet Outcomes (UPMC Series)

• CMV infection in 170/607 (28%). UL97 mutations 9.4% (16/170); also 4/16 UL54
• 12% cleared successfully; 31% failed; 51% cleared but relapsed with viremia
• 87% (14/16) foscarnet; 78% developed toxicity
• 11/16 had CMV pneumonitis; 4/16 (25%) died; high viral load assoc with mortality.

Foscarnet Outcomes
(Johns Hopkins series)

• Retrospective study of transplant recipients treated with foscarnet for CMV, 2005-15
• 39 pts (22 SOT, 17 HSCT); 38.5% had GCV resistance; 28% tissue-invasive CMV
• Median duration of FOS was 32 days. Virologic failure in 13/39 (33%).
• Mortality 31% (higher in HSCT)

(Avery R et al, Transplantation 2016; 100:e74-e80)
Foscarnet Outcomes
(Johns Hopkins series)

• GCV resistance more common in SOT than HCT, although mortality higher in HCT
• Renal dysfunction in 51% by end of treatment, and persisted in 28%, 6 mos later
• Conclusion: Outcomes of existing treatment for resistant/refractory CMV are suboptimal in terms of virologic clearance, renal dysfunction, and mortality.
Newer Options for GCV-R CMV

- (Off-label: Leflunomide)
- Investigational: Brincidofovir (CMX001)
- Investigational: Maribavir
- Investigational: Letermovir (AIC246)
- Adoptive immunotherapy (including 3rd party donor CMV-specific T cells)
Leflunomide
Leflunomide for CMV
(Cleveland Clinic Series)

• 17 patients with complex CMV syndromes
• 14 had viral load responses to leflunomide
• 9 achieved long-term viral suppression (Avery et al, Transplantation 2010; 90:419-426)
• Toxicities include anemia, thrombocytopenia, LFT’s, diarrhea, nausea, neuropathy
• Since that time, less successful
Structures of Cidofovir and Brincidofovir (CMX001)
### Brincidofovor Activity Against dsDNA Viruses

<table>
<thead>
<tr>
<th>Viral Family</th>
<th>Virus</th>
<th>Brincidofovor EC&lt;sub&gt;50&lt;/sub&gt; (µM)</th>
<th>Cidofovir EC&lt;sub&gt;50&lt;/sub&gt; (µM)</th>
<th>Ganciclovir* EC&lt;sub&gt;50&lt;/sub&gt; (µM)</th>
<th>Foscarnet EC&lt;sub&gt;50&lt;/sub&gt; (µM)</th>
<th>Acyclovir EC&lt;sub&gt;50&lt;/sub&gt; (µM)</th>
<th>Maribavir EC&lt;sub&gt;50&lt;/sub&gt; (µM)</th>
<th>Letermovir EC&lt;sub&gt;50&lt;/sub&gt; (µM)</th>
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<td>Herpes</td>
<td>Cytomegalovirus (CMV)</td>
<td>0.001</td>
<td>0.4</td>
<td>3.8</td>
<td>50-800</td>
<td>&gt;200</td>
<td>0.31</td>
<td>0.005</td>
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<td>Epstein-Barr Virus (EBV)</td>
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<td>65.6</td>
<td>0.9</td>
<td>&lt;500</td>
<td>6.2</td>
<td>0.63</td>
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<td>Human Herpesvirus 6A (HHV-6A)</td>
<td>0.003</td>
<td>2.7</td>
<td>5.8</td>
<td>16</td>
<td>10</td>
<td>Inactive</td>
<td>&gt;10</td>
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<tr>
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<td>Human Herpesvirus 8 (HHV-8)</td>
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<td>8.9</td>
<td>177</td>
<td>&gt;100</td>
<td>Inactive</td>
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<td>Herpes Simplex Virus 1 (HSV-1)</td>
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<td>3.0</td>
<td>0.7</td>
<td>92-95</td>
<td>3.8</td>
<td>Inactive</td>
<td>&gt;10</td>
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<td></td>
<td>Herpes Simplex Virus 2 (HSV-2)</td>
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<td>6.5</td>
<td>2.5</td>
<td>91-96</td>
<td>4.4</td>
<td>Inactive</td>
<td>&gt;10</td>
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<td>Varicella Zoster Virus (VZV)</td>
<td>0.0004</td>
<td>0.5</td>
<td>1.3</td>
<td>39.8</td>
<td>3.6</td>
<td>Inactive</td>
<td>&gt;10</td>
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<td>Adenovirus</td>
<td>Adenovirus 7 (AdV7)</td>
<td>0.02</td>
<td>1.3</td>
<td>4.5-33</td>
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<td>&gt;100</td>
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<td>&gt;10 (AdV2)</td>
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<td>Polyoma</td>
<td>BK Virus (BKV)</td>
<td>0.13</td>
<td>115</td>
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<td>&gt;200</td>
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<td>JC Virus (JCV)</td>
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<td>Human Papillomavirus 11 (HPV-11)</td>
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<td>716</td>
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<td>Vaccinia</td>
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<td>Inactive</td>
<td>&gt;144</td>
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</table>

EC<sub>50</sub> = concentration in µM required to reduce viral replication by 50% *in vitro*.  
Data are compiled from multiple sources and include multiple materials and methodologies.  
*Valganciclovir is rapidly converted to ganciclovir *in vivo*. Therefore, ganciclovir is the relevant compound for cell activity studies.
Brincidofovir Phase 3 HSCT Prophylaxis Study

• Oral cidofovir analogue, dosed 2x/wk, lacks nephrotoxicity of IV cidofovir
• SUPPRESS: Phase 3 randomized trial of 14 wks brincidofovir prophylaxis vs placebo in HSCT
• Failed to meet primary endpoint of prevention of CMV infection through Week 24; more GI GVHD and steroid use in the brincidofovir arm (Marty F et al, BMT Tandem Meeting, Feb 2016)
Maribavir (SHP620)

Benzimidazole with novel mechanism: inhibits UL97 protein kinase; inhibits viral encapsidation, nuclear egress of viral particles
Maribavir

• Inhibits CMV and EBV (not HSV/VZV)
• No renal, hepatic, or hematologic toxicity
• Major side effect is dysgeusia
• Phase 3 prophylaxis trials in HSCT and liver transplant failed (using dose 100 mg BID)
• E-IND cases: 6 recipients with refractory CMV: some responses at doses of 400 – 800 mg BID (Avery RK et al, Transpl Infect Dis 2010; 12:489-496)
Maribavir E-IND Patient #2
(Avery et al, Transpl Infect Dis 2010; 12:489-496)

- Lung transplant recipient, CMV D+/R-, had GCV-R CMV with UL97 mutation, treated with foscarnet c/by renal failure, cleared temporarily
- 5 mos later had steroid pulse for rejection, and GCV-R CMV recurred with pneumonitis and peak VL 250,000. This time refractory to FOS/GCV, CMV Ig, LEF; Cr judged too high for cidofovir
Maribavir E-IND Patient #2

• Maribavir was obtained via emergency IND
• Starting dose was 400 mg po BID; starting CMV VL around 60,000 c/ml
• Cyclosporine also changed to sirolimus
• Within 7 days, CMV viral load was undetectable and remained so for >4 yrs; maribavir discontinued after 6 mos
• Maribavir Patient #5 (intestinal transplant) similar striking response
E-IND Patient #4: 
Maribavir Resistance

• Patient #4 (heart transplant recipient with very high viral load) developed viral UL97 mutations T409M and H411Y, which confer maribavir resistance (Strasfeld L et al, JID 2010; 202:104-8)

• Maribavir resistance can also occur at UL27; pUL27 has nucleolar localization but with resistance mutations, loses this localization and is found in cytoplasm (Hakki M, Antiviral Res 2011; 92:313-8)
Maribavir Phase 2 Trials

• Study 202: Randomized 1:1:1, blinded trial of 3 doses of maribavir (400 mg, 800 mg, 1200 mg BID) for resistant/refractory CMV

• Study 203 (Europe): Randomized controlled trial of maribavir vs valganciclovir for uncomplicated CMV

• (Abstract presentations at ID Week 2016, BMT Tandem Meetings 2017, Am Transplant Congress 2017)
Maribavir Study 202 (Resistant/Refractory CMV)

• Randomized trial of maribavir 400 mg, 800 mg, 1200 mg BID in SOT or HSCT patients who had failed previous therapies
• Primary endpoint: viremia clearance at 6 wks
• Treatment could continue up to 24 wks
• Secondary endpoints: time to first undetectable CMV PCR, time to recurrence

(Pereira M et al, Am Transplant Congress, May 2017, Chicago, IL)
Maribavir Study 202 (Resistant/Refractory CMV)

- 70 SOT (60.8%), 47 HSCT (39.2%) randomized
- Viremia clearance similar between all doses (66.7% overall)
- No difference between SOT and HSCT
- Median time to first undetectable CMV PCR was 23 d (no difference between doses)
- 30/86 (34.9%) had a recurrence (Pereira M et al, Am Transplant Congress, May 2017, Chicago, IL)
Maribavir Study 202 (Resistant/Refractory CMV)

• Adverse effects: Dysgeusia in 65% overall, nausea 34%; overall favorable safety profile
• Although no placebo arm, no evidence of myelosuppression or nephrotoxicity
• Two Phase 3 multicenter studies now in progress: Study 303 (Resistant/Refractory) and Study 302 (Pre-Emptive Therapy in HSCT)
Letermovir (MK-8228, AIC246)

Oral or IV, potent, selective terminase inhibitor
First Report Of Letermovir For Treatment

- Lung recipient with tissue-invasive CMV involving lungs, GI treat, retina (U Mich)
- Refractory to all known drugs including leflunomide and brincidofovir
- Obtained letermovir from AiCuris via E-IND; resulted in rapid clinical, virological, and radiological resolution of disease. (Kaul D et al, Am J Transplant 2011; 11:1079-84)
Letermovir Phase 3 HSCT Prophylaxis Trial
(Marty F et al, BMT Tandem Meeting Feb 2017)

• Phase 3, double-blind, placebo-controlled trial
• Randomized 2:1 letermovir 480 mg/d vs placebo through Week 14 after HSCT
• Primary endpoint was the proportion with clinically significant (CS) CMV through 24 wks
• Of 495 subjects, fewer in the LET group (122/325, 38%) had CS CMV or failure at 24 wks, c/w 103/170 (61%) placebo (p<0.0001)
Figure 1. Time to Onset of Clinically Significant CMV Infection

Subjects with undetectable CMV DNA at Randomization

Letermovir vs. Placebo
Stratified log-rank test,
One-sided $p=0.0005$
Questions Which Remain

• Will this change strategy in HSCT programs (traditionally was pre-emptive therapy?)
• Letermovir for treatment? Only 1 case report
• Will different drugs have different roles?
• Combination therapy? (Maribavir and GCV are antagonistic, but other combinations?)
• Cost-effectiveness?
Other New Frontiers

• CMV-specific T cell therapy (including 3rd party) – promising, but labor and time-intensive

• Use of CMV-specific immune function tests (CMV T-spot, CMV IGRA) for monitoring, risk stratification, duration of prophylaxis

• CMV vaccines? (HSCT trial data being analyzed; Kidney transplant D+/R- study completed)
Conclusions

• Current treatment for CMV is largely valganciclovir- or ganciclovir-based therapy. Treatment is successful in the majority, but a significant fraction of patients experience toxicity (especially neutropenia) and some develop resistant or refractory CMV.

• Other licensed drugs (foscarnet, cidofovir) are characterized by high toxicity risk and suboptimal outcomes.
Conclusions

• Several investigational drugs have potential utility for prophylaxis and/or treatment of CMV.

• From the clinician’s standpoint, we need to expand the armamentarium, ideally with all of these drugs; this represents an unmet need in transplant recipients.

• Robust enrollment in ongoing and future clinical trials is very important.
THANK YOU

- Thank you to the organizers of this meeting for inviting me
- Thank you to the audience for your attention!
- Questions?