

Adenovirus, BK virus, CMV New

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Minireview

The “ABC” of Virus-Specific T Cell Immunity in Solid Organ Transplantation

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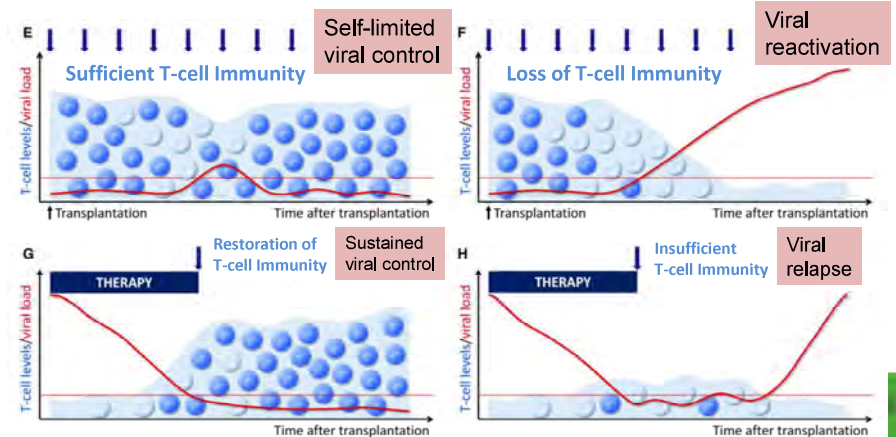
interferon- γ ; ICS, intracellular cytokine staining;
LTag, large T antigen; PBMC, peripheral blood
mononuclear cells; PTLD, posttransplant lymphoproliferative disorder; PyVAN, BKPyV-associated
nephropathy; SOT, solid organ transplantation; VZV, varicella zoster virus

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Introduction

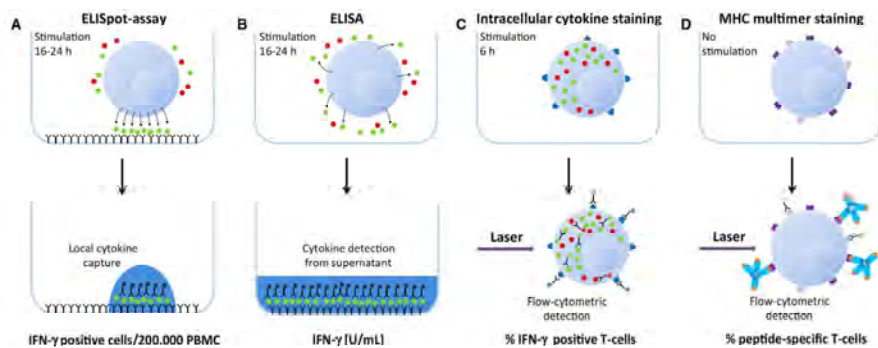
Transplant recipients are at increased risk of infectious
complications because the immunosuppression needed

Dynamics of virus-specific T cells & Viral loads



Sester M. Am J Transplant. 2016 Jun;16(6):1697-706.

Techniques for Detection of Virus-specific T cells



IFN- γ

Other cytokines

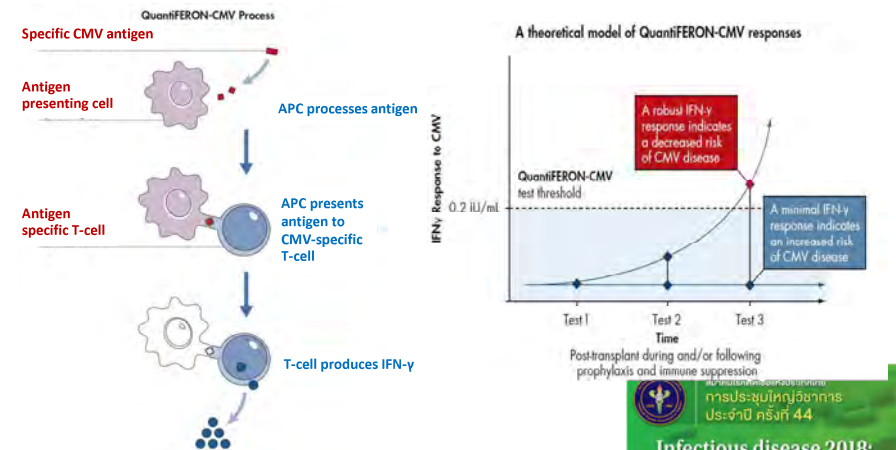
Cell surface molecule

Phenotypical Markers

Infectious disease 2018:
Now and Next

Sester M. Am J Transplant. 2016 Jun;16(6):1697-706.

QuantiFERON-CMV

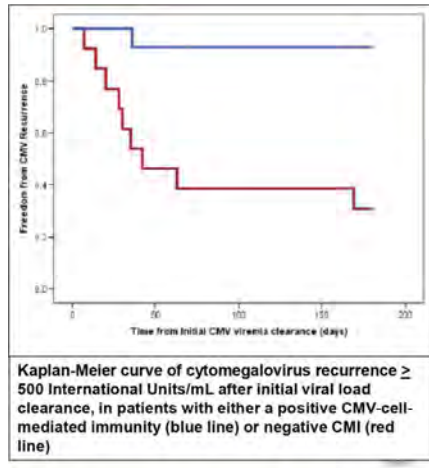


www.qiagen.com

Infectious disease 2018:
Now and Next

CMV-specific Cell-mediated Immunity to "Personalize CMV Therapy" in SOT

- At end of Rx (VL negative)
- 14/27 (51.9%) had a **QuantiFERON-CMV (+)** and had antivirals discontinued
 - 1 low-level asymptomatic recurrence
- 13/27 (48.1%) had a **QuantiFERON-CMV (-)** and received 2 months of 2' prophylaxis
 - recurrence in 69.2% ($p=0.001$)

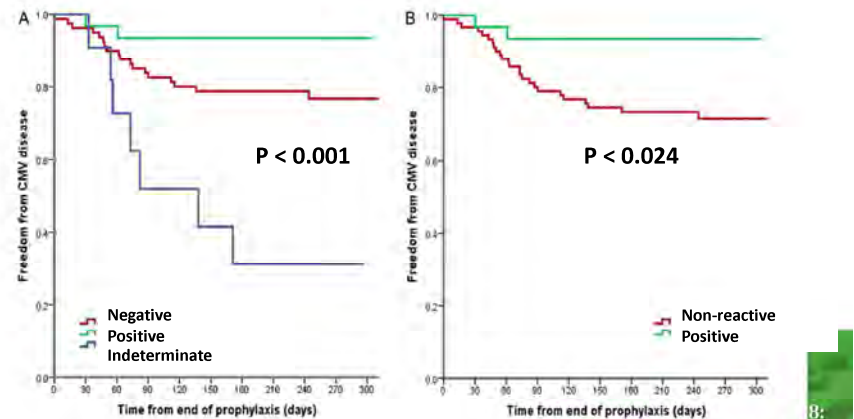


Kumar D. Am J Transplant. 2017 Sep;17(9):2468-2473.

Now and Next

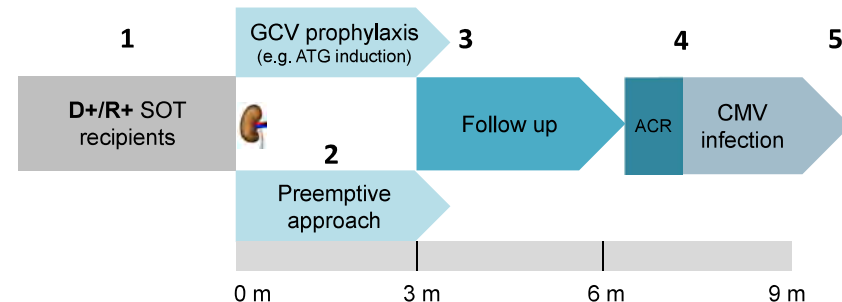
CMV-specific Cell-mediated Immunity to "Personalize CMV Prophylaxis" in SOT

The result of QuantiFERON-CMV assay at the end of prophylaxis in High-risk SOT (D+/R-)Recipients



Manuel O. Clin Infect Dis. 2013 Mar;56(6):817-24

Potential Use of CMV-specific Immunity Assay



Adapted from Kotton CN, et al. Transplantation. 2018 Jun;102(6):900-931.

Now and Next

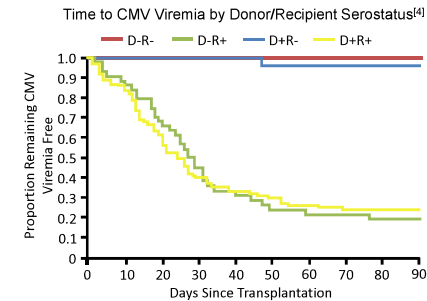


CMV Antiviral Agents in HSCT

| FDA-Approved Agents | | | |
|--|------------------------------|---------|--|
| Agent | MoA | Dosing | Considerations |
| Letermovir | CMV UL56-binding agent | Oral | Approved for CMV prophylaxis |
| Ganciclovir* | Target CMV polymerase | IV | Recommended for first-line preemptive therapy |
| Valganciclovir* | | Oral | |
| Foscarnet* | Target CMV polymerase | IV | Recommended when ganciclovir/valganciclovir resistance/intolerance |
| Cidofovir* | | IV | |
| Val/acyclovir | Target CMV polymerase | IV/oral | Limited activity against CMV disease |
| Late-Phase Investigational Agents/Approaches | | | |
| Brincidofovir | Lipid conjugate of cidofovir | Oral | Phase III studies |
| Maribavir | CMV UL97-binding agent | Oral | Phase III studies |
| CMV CTLs | Varied | IV | Phase II/III studies |
| CMV vaccines | Varied | IV | Phase II/III studies |

*Approved for treating CMV retinitis in pts with AIDS.

Risk of CMV infection in HSCT Recipients



Cord blood transplant: ~ 80%^[1]

Allogeneic HCT

Adult: ~ 50% (range: 40% to 80%)^[2]

Pediatric: ~ 30%^[3]

10% to 30% of seropositive recipients develop CMV disease

Prior to effective antivirals, 25% to 30% mortality associated with CMV disease

1. Lau C, et al. BMT Tandem 2017, Abstract 228.
2. Chan ST, et al. Blood Rev. 2017;31:173-183.
3. Qayed M, et al. Pediatr Blood Cancer. 2015;62:364-366.
4. Panagou E, et al. Transpl Infect Dis. 2016;18:405-414.



Letermovir FDA Approved for CMV Prophylaxis

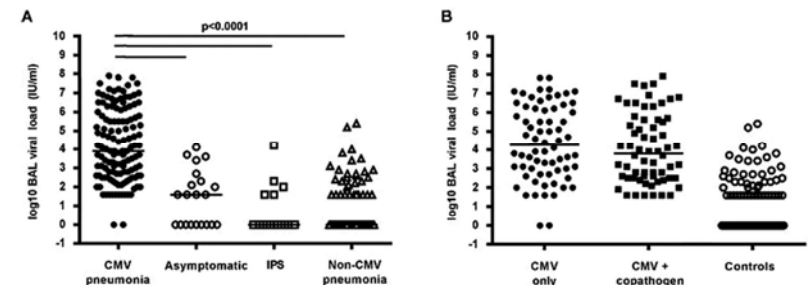
- Indication: prophylaxis of CMV infection and disease in adult **CMV-seropositive recipients** of an allogeneic HCT

| Section | Recommendation |
|---------------------------------|--|
| Dosing | <ul style="list-style-type: none"> Forms: tablet or injection 480 mg QD (1 tablet PO or IV infusion over 1 hr) Initiate between Days 0 and 28 post transplantation (before or after engraftment); continue through Day 100 post transplantation |
| Dose adjustments | <ul style="list-style-type: none"> If coadministered with cyclosporine, reduce letermovir to 240 mg QD |
| Contraindications | <ul style="list-style-type: none"> Pimozide Ergot alkaloids Pitavastatin/simvastatin (coadministered with cyclosporine) |
| Monitoring for CMV reactivation | <ul style="list-style-type: none"> Recommended following completion of prophylaxis |

Letermovir [package insert]. November 2017.



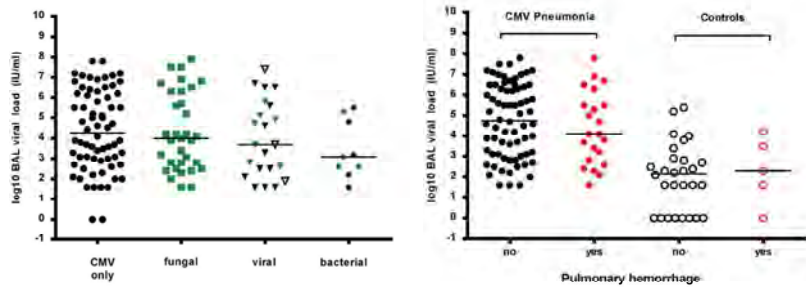
BAL Fluid CMV load from HSCT recipients with CMV Pneumonia (1)



Boeckh M. J Infect Dis. 2017 May 15;215(10):1514-1522.



BAL Fluid CMV load from HSCT recipients with CMV Pneumonia (2)



Boeckh M. J Infect Dis. 2017 May 15;215(10):1514-1522.



Diagnostic Consideration: CMV Pneumonitis

- CMV shedding in the lower respiratory tract does occur and therefore a low CMV DNA load might well represent asymptomatic infection
- A negative plasma/whole blood PCR or the absence of CMV inclusions do not exclude the diagnosis

Detected BAL CMV load \neq (not always) CMV pneumonitis

