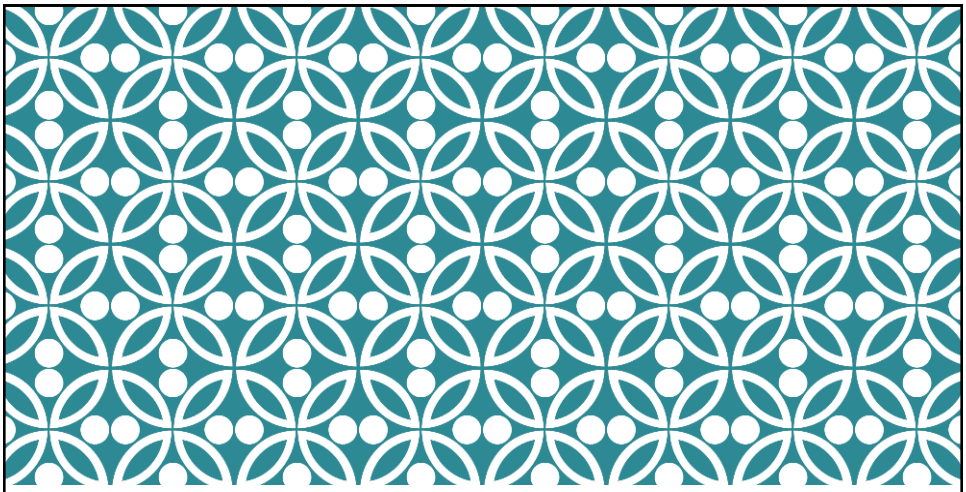


CMV TREATMENT AND THE DILEMMA OF RESISTANCE

Alissa Jade Wright, MD, FRCPC, MSc
AMMI Canada Merck Integrated Symposium
May 4, 2017

DISCLOSURES

Educational grant money
- UBC-Pfizer
- UBC-Sunovion

Advisory board
- Merck
- Pendopharm

Speaker fees
- Astellas
- Merck

OBJECTIVES

Review the current approaches to treatment of CMV disease for SOT and HSCT patients.

Discuss treatment challenges associated with patients with CMV resistance.

CASE

45M s/p allogeneic HSCT for AML

- 10/10 matched VUD, CMV D-/R-

Post-transplant

- Recurrent infections → antibiotics + IVIG
- Developed cGVHD including BOS (O_2 dependent)

Accepted for lung transplant

- Serology: CMV D+/R+

QUESTION 1: WHAT IS THIS PATIENT'S RISK FOR CMV POST-LUNG TRANSPLANT?

1. High risk because he is a lung transplant recipient
2. Intermediate risk because of the previous HSCT
3. High risk because he is CMV seronegative (D+/R-)
4. Intermediate risk because he is CMV seropositive (D+/R+)

CMV RISK FACTORS

Risk of CMV	SOT Serostatus	HST Serostatus
High (30-80%)	D+/R-	D+/R+, D-/R+
Intermediate (5-30%)	D+ /R+ > D-/R+	D+/R-
Low (<5%)	D-/R-	D-/R-

Lung or intestinal transplant

Haploidentical or UCBT

T-cell-depleted graft

IS/Chemo regimen
- ATG, alemtuzamab, fludarabine

Leukopenia, lymphopenia

aGVHD

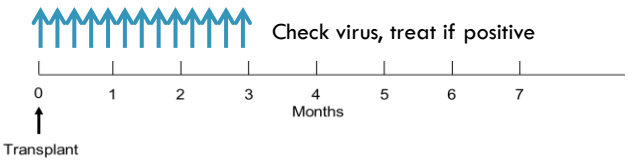
Graft rejection

} Cellular immunity

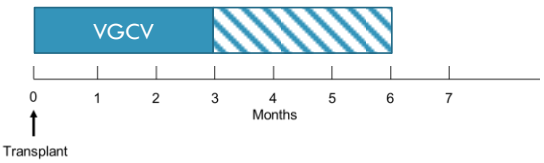
Razonable et al. AJT 2013. Ljungman, Snydman, & Boeckh. Transplant Infections. 2016. Ariza-Heredia et al. Canc. Lett. 2014. Panagou et al. TID. 2016.

POST-TRANSPLANT MANAGEMENT STRATEGIES

1. Prevention – leukoreduced blood for CMV -/-
2. Pre-emptive therapy



3. Prophylaxis



Hybrid?

Adapted from Razonable et al. AJT 2013

GUIDELINE RECOMMENDATIONS

SOT

- Universal prophylaxis favoured for D+/R-
  - Duration 3-12 months
- Either strategy for R+

HSCT

- Pre-emptive therapy currently favoured
- Drug toxicity limits prophylaxis
- Screen weekly from day 10 to 100

Kotton et al. Transplantation. 2013. Zaia et al. BMT. 2009.

CASE

Receives 6 months of VGCV + monthly IVIG

Two months later, clinic follow-up

- c/o intermittent non-bloody diarrhea & abdominal cramping
- CMV PCR 20,000 IU/mL
- WBC 3.9 (1.5), AST/ALT N, Cr 75
- Stool studies negative

QUESTION 2: THIS PATIENT HAS

1. Asymptomatic DNAemia
2. CMV tissue invasive disease (GI)
3. Diagnosis depends on endoscopy + CMV PCR of tissue
4. Diagnosis depends on endoscopy + histopathology

COMPLICATIONS

Direct Effects

CMV Viral Syndrome

- T>38°C, malaise, leukopenia, atypical lymphocytes, thrombocytopenia, elevated ALT/AST

  PLUS

- CMV detected in blood

  ONLY FOR SOT

Tissue Invasive Disease

- GI – colitis, hepatitis
- Pneumonia
- Retinitis…

CAN BE PROVEN OR PROBABLE

Indirect Effects

Bacterial, viral or fungal infections

PTLD

Cardiovascular events

New-onset DM

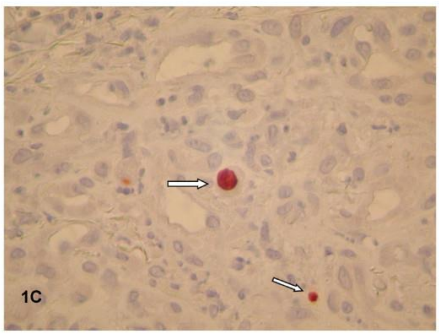
Immunosenescence

Acute and chronic rejection

Mortality

Kotton. AJT. 2013. Humar et al. AJT. 2006. Ljungman et al. CID. 2017.

DIAGNOSIS



Cannot use CMV IgG

Diagnostic tests of choice

- PCR of plasma
- Biopsy of affected organ(s)
  - Histopathology + immunostaining/in situ hybridization

CMV pneumonia

- BAL PCR may be disease vs. shedding = possible CMV

CMV GI disease

- Disease may still occur with negative blood PCR
- Tissue PCR alone may be disease vs. shedding = possible CMV

Kotton et al. Transplantation 2013. Hohenthal et al. Eur J Haematol. 2005 Goodgame et al. Am J of Gastroenterol. 1993

QUESTION 3: I WOULD START

1. Ganciclovir 5 mg/kg IV BID
2. Valganciclovir 900 mg PO BID
3. Ganciclovir 5 mg/kg IV BID + CMV IgG
4. Valganciclovir 900 mg PO BID + CMV IgG

TREATMENT OPTIONS

(Val)ganciclovir
- Available
- Main toxicities: myelosuppression

Foscarnet
- Special Access Program
- Main toxicities: Electrolyte disturbance, renal failure

Cidofovir
- Special Access Program
- Main toxicities: Renal failure, uveitis

Oral Valganciclovir Is Noninferior to Intravenous Ganciclovir for the Treatment of Cytomegalovirus Disease in Solid Organ Transplant Recipients

A. Åsberg[a,‡], A. Humar [b,‡], H. Rollag[c], A. G. Jardine[d], H. Mouas[e], M. D. Pescovitz[f], D. Sgarabotto[g], M. Tuncer[h], I. L. Noronha[i] and A. Hartmann[j,*] on behalf of the VICTOR Study Group[†]

American Journal of Transplantation 2007; 7: 2106–2113

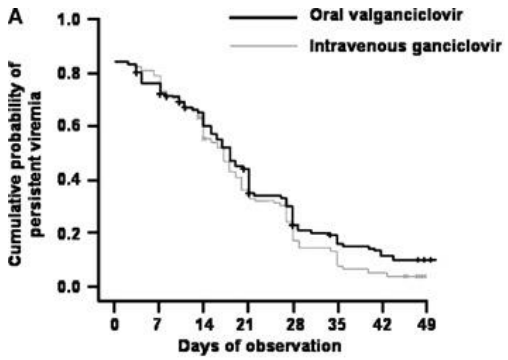
326 patients randomized

PO VGCV vs. IV GCV

"Non-life threatening"

Predominantly:

- Kidney Tx recipients
- CMV syndrome > colitis



TREATMENT

First line therapy

- VGCV (900 mg every 12 hours) or IV GCV (5 mg/kg every 12 hours)

In SOT, VGCV is preferred except

- Life-threatening disease
- Poor oral drug bioavailability
- Medication non-adherence

In HSCT, cohort data suggests VGCV can be used safely for pre-emptive treatment

- Noninferiority RCT terminated for low accrual
- GCV still has best evidence

Kotton et al. Transplantation 2013. Violin et al. Bone Marrow Transplant. 2008.

CMV IGG (CYTOGAM) OR IVIG

Ljungman et al. CID. 1992.a

Reduced Mortality of Cytomegalovirus Pneumonia After Hematopoietic Cell Transplantation Due to Antiviral Therapy and Changes in Transplantation Practices

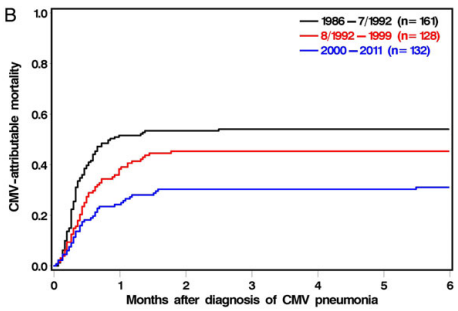
Clinical Infectious Diseases® 2015;61(1):31–9

Examined patients at FHCRC from 1986-2011

Diagnosis per standard criteria

421 recipients

- 30% 6 mo. survival
- 296 deaths
  - 63% from CMV
- Antivirals reduced mortality
  HR 1.9 (95% CI 1.2–3.2)
- No improvement in mortality with Ig



CASE

CMV VL

- Week 1 CMV 20,000
  - Treatment initiated 3 days after blood drawn
- Week 2 CMV 78,000
- Week 3 CMV 40,500
- Week 4 CMV 18,000
- …

QUESTION 4: I AM CONCERNED ABOUT DRUG RESISTANCE

1. True
2. False

Rising pp65 antigenemia during preemptive anticytomegalovirus therapy after allogeneic hematopoietic stem cell transplantation: risk factors, correlation with DNA load, and outcomes

W. Garrett Nichols, Lawrence Corey, Ted Gooley, W. Lawrence Drew, Richard Miner, Meei-Li Huang, Chris Davis, and Michael Boeckh
BLOOD, 15 FEBRUARY 2001 • VOLUME 97, NUMBER 4

119 allogeneic HSCT patients
- 1995-1997 at FHCRC

45% had a rise in antigenemia after Rx started
- Correlated with CMV VL
- 39% 2x & 28% ≥5x
- 43% within 1 week → 47% → 6% → 4% after 4+ weeks

- 15 patients had susceptibility testing
  - 20/21 isolates GCV sensitive
- RF for rise: corticosteroids
  - OR 4.0 if 1-2 mg/kg
  - OR 10.1 if ≥2 mg/kg

Rising pp65 antigenemia during preemptive anticytomegalovirus therapy after allogeneic hematopoietic stem cell transplantation: risk factors, correlation with DNA load, and outcomes

W. Garrett Nichols, Lawrence Corey, Ted Gooley, W. Lawrence Drew, Richard Miner, Meei-Li Huang, Chris Davis, and Michael Boeckh
BLOOD, 15 FEBRUARY 2001 • VOLUME 97, NUMBER 4

Of 47 patients with rising values
- 15 re-induced, 32 maintenance

If re-induced, next value was lower & no CMV disease

If not re-induced
- 4 patients developed CMV disease on treatment
- 3/4 patients died of CMV disease

At the time, only 1 week "induction Rx" used
- Suggestion was to increase antiviral dose

TREATMENT

Weekly PCR during therapy for monitoring

- Half life ~3-4 days → no benefit increased testing

Continue until 2 negative assays one week apart (min. 2 weeks)

Viral load kinetics

1. Predict outcome
   - ⩾1-log drop at day 7 = lower risk of recurrence (8.7 vs. 34.5%)
2. Do not predict for drug resistance early on
   - Reflect immune response

Humar et al. J Infect Dis. 2002. Roberts et al. J Infect Dis. 1998.

TREATMENT TIPS

1. Consider IS reduction (esp. if severe dz)
2. Account for delay in therapy initiation when assessing response
   - Median doubling times for SOT
   - 1.54 days for D+/R-
   - 2.67 days for D+/R+
3. Induction and maintenance dosing are likely no longer relevant → treatment dose or prophylaxis
4. Do not dose reduce for leukopenia
5. **Careful dosing if AKI/CKD**

Atabani et al. AJT 2012.

CASE

Viral load slowly fell to <526 IU/mL

- No negative values
- Patient continued on valganciclovir

Low level DNAemia for 9+ months

- Small decline in renal function CrCl 58 ml/min
- Dose reduced to 450 mg po BID

CMV PCR <526 → 6,200

CASE

No symptoms, laboratory work unchanged

Patient admitted for high dose GCV

- 10 mg/kg IV BID

CMV PCR

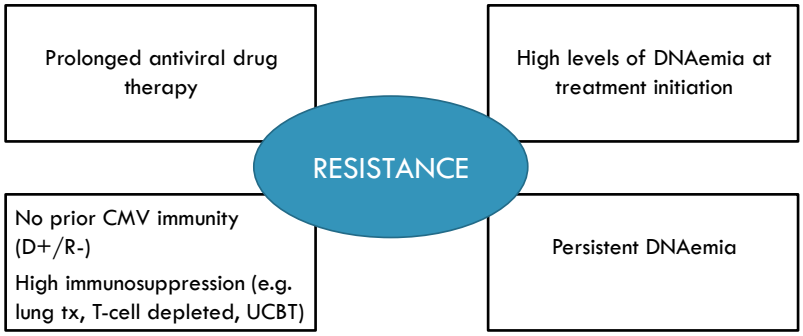
- Week 1 CMV 6,200
  - Treatment initiated 1 day after blood drawn
- Week 2 CMV 21,800
- Week 3 CMV 18,100
- Week 4 CMV 22,000

QUESTION 5: I AM CONCERNED ABOUT DRUG RESISTANCE

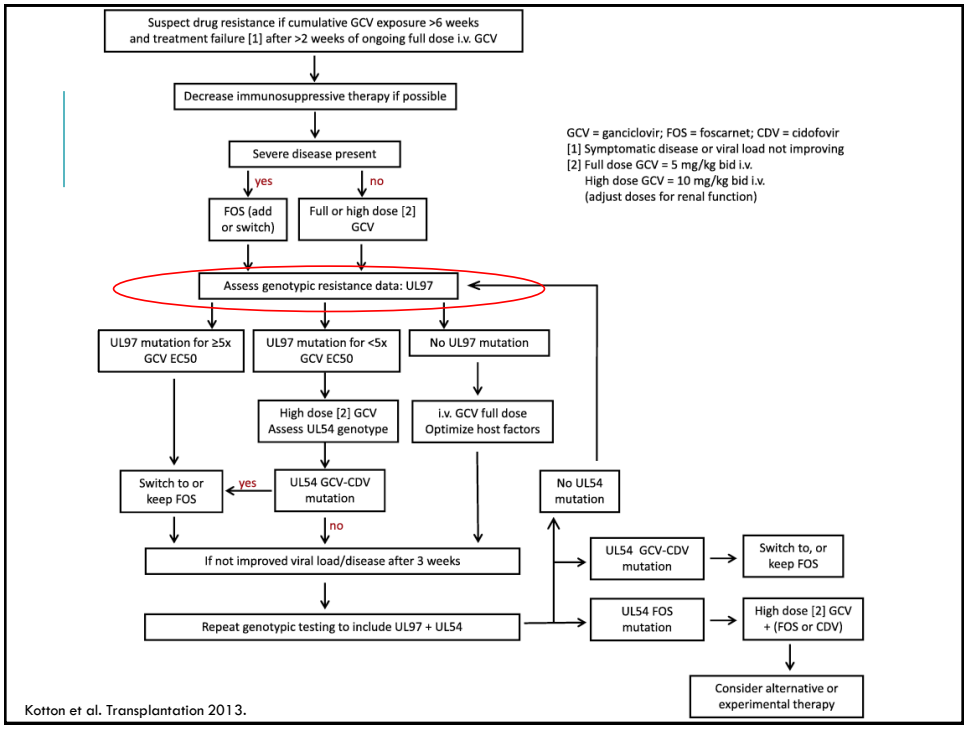
1. True
2. False

DRUG RESISTANT VIRUS?

Unchanged/rising viral loads after >2 weeks of full dose therapy



Kotton et al. Transplantation. 2013. Boeckh & Ljungman. Blood. 2009.



Kotton et al. Transplantation 2013.

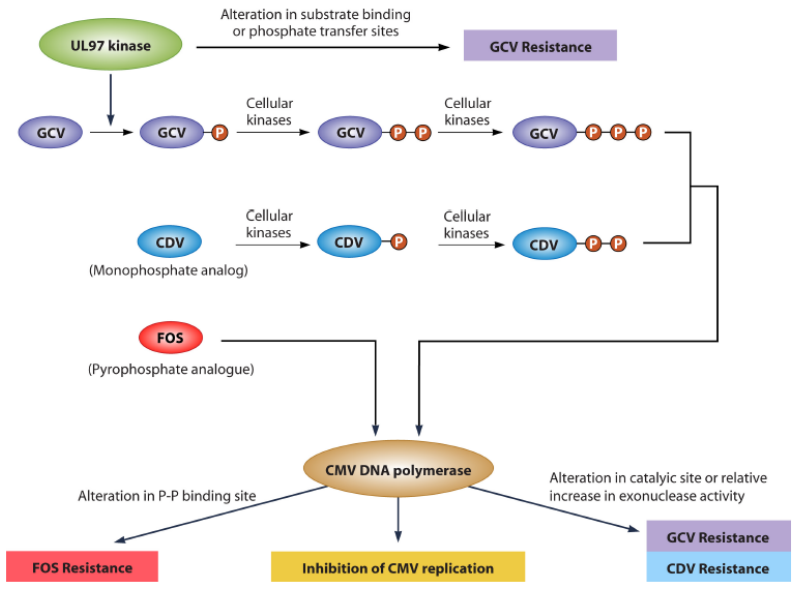
CASE

Blood sent to National Lab for resistance testing

- Positive UL97 mutation (L595S)
- Unable to amplify UL54 region

QUESTION 6: AT THIS POINT, I WOULD

1. Keep going with high-dose GVC
2. Change to foscarnet
3. Change to cidofovir
4. Phone a colleague and ask for advice



Lurain & Chou. Clin Micro Rev. 2010

UL97 GENOTYPES

Fold change in EC_{50}	5-15x	2-5x	<2x
Most common	M460V/I, H520Q, A594V, **L595S**, C603W	C592G	
Less common	M460T, A594G, 595del, 596del, L595F/W, K599T, C603R, C607Y, del(Q3)	A594E/T, E596G, C603S, 600del2, C607F	A591V, N597D, K599E/R, L600I, 600del, T601M, D605Ed

Only able to use high-dose GVC if <5x change in EC_{50}

~90% of the time, occur before UL54 mutations

Kotton et al. Transplantation 2013. Smith et al. J of Infect Dis. 1998.

CASE

Patient changed to foscarnet

CMV declined to <526 x 6 weeks

- Finally 2 negative values
- Immediately after d/c, positive again
- Remained stable <526 IU/mL off treatment

Two months later, decline in spirometry

- BAL negative
- Team suspects rejection
- Pulse steroids initiated
- CMV rises to 13,100
- Patient admitted for foscarnet

CASE

On foscarnet

- Week 2 CMV 35,200 → UL54 typing requested
- Week 3 CMV PCR 13,200
- Week 4 CMV PCR 21,000
- Week 5 CMV PCR 9,400

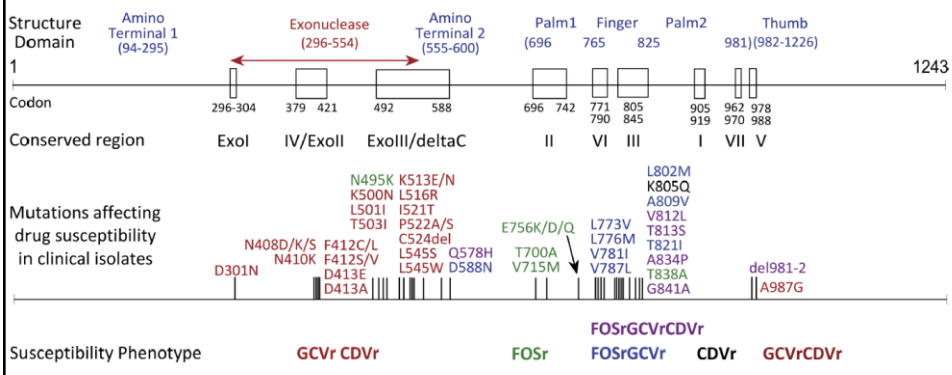
UL54 typing returns

- Positive for Q578H

QUESTION 7: AT THIS POINT, I WOULD

1. Continue on with foscarnet.
2. Change to cidofovir
3. Look for alternative agents (activated T-cells, maribavir)
4. Phone a colleague and ask for advice

UL54 GENE MAP



Kotton et al. Transplantation 2013.

GENOTYPIC VS. PHENOTYPIC

Phenotypic plaque reduction assay (PRA)

- Gold standard
- Slow (4-6 weeks) & labour-intensive

Genotypic analysis

- Quick
- Falsely negative if subpopulation <20-30%
- Difficult to interpret due to natural polymorphisms

Q578H

- NML report: "published reports… contentious with regards to sensitivity to ganciclovir and cidofovir"

Chaer et al. Blood. 2016.

NOVEL THERAPIES

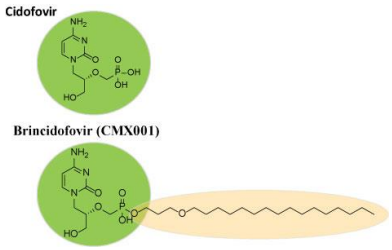
Drugs

- Brincidofovir
- Maribavir
- Letermovir

Immunotherapies

- Activated CMV-specific T-cells
- Vaccines (prevention)

BRINCIDOFOVIR



Similar MOA to cidofovir

- Higher cellular concentrations → less nephrotoxicity
- Cross-resistance

Failed phase 3 clinical trial for CMV prophylaxis post-HSCT (SUPPRESS trial)

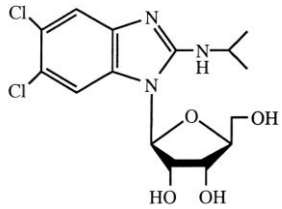
- Many subsequent planned trials have been withdrawn

Few case reports in resistant/refractory CMV infections

- Failed if UL54 mutation present for CDV-R

El-Haddad et al. Antiviral Res. 2016. Tippin et al. Ther Drug Monit. 2016.

MARIBAVIR



Inhibits UL97 kinase & viral DNA synthesis
- No cross-resistance
- Antagonistic with GCV/VGCV

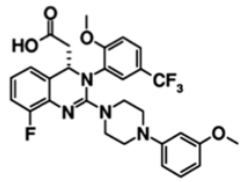
Success in case series of GCV-resistant CMV infections
- May not completely inhibit DNAemia

Failed phase 3 clinical trial for CMV prophylaxis post-HSCT
- Suboptimal dosage? Wrong endpoint?

Two trials in Canada starting
- RCT of VGCV vs. maribavir in HSCT
- Phase 3 multicenter trial for refractory/resistant CMV infections in transplant patients

Komazin et al. J. Virol. 2003. Marty et al. Lancet Infect Dis. 2011. Avery et al. TID. 2010. Marty & Boeckh. Curr Opin Virol. 2011.

LETERMOVIR



Inhibits UL56 (CMV terminase complex)
- Converts concatemeric progeny DNA → small genomes for packaging
- No cross-resistance

Single case reports of success in refractory/resistant CMV infections
- PCR may be slow to decline because does not inhibit synthesis

Letermovir resistance mutations already detected
- Low genetic barrier to resistance?

Success in phase 3 clinical trial for CMV prophylaxis post-HSCT (NCT02137772)
- New standard of care?

Kaul et al. AJT. 2011. Chou. Antimicrob Agents Chemother. 2015.

ACTIVATED T-CELLS

Attractive for multiple viral infections, including CMV

Significant logistical issues

- E.g. availability, cost, time delay to generate cells, research protocol
- Donor-derived vs. third party

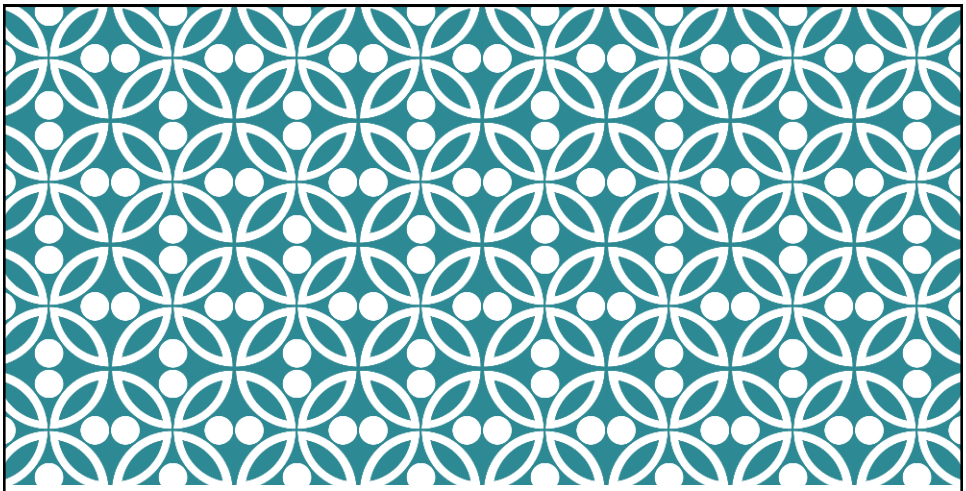
Best evidence in HSCT population

- Donor may be easily available

More difficult in SOT because of IS

- CNIs prevent activation of cytokine genes in T cells → lack of efficacy

Arasaratnam & Leen Ann Transl Med. 2015. Uhlin et al. CID. 2012.



QUESTIONS?

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Lurain NS1, Chou S. Antiviral drug resistance of human cytomegalovirus. Clin Microbiol Rev. 2010 Oct;23(4):689-712.

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