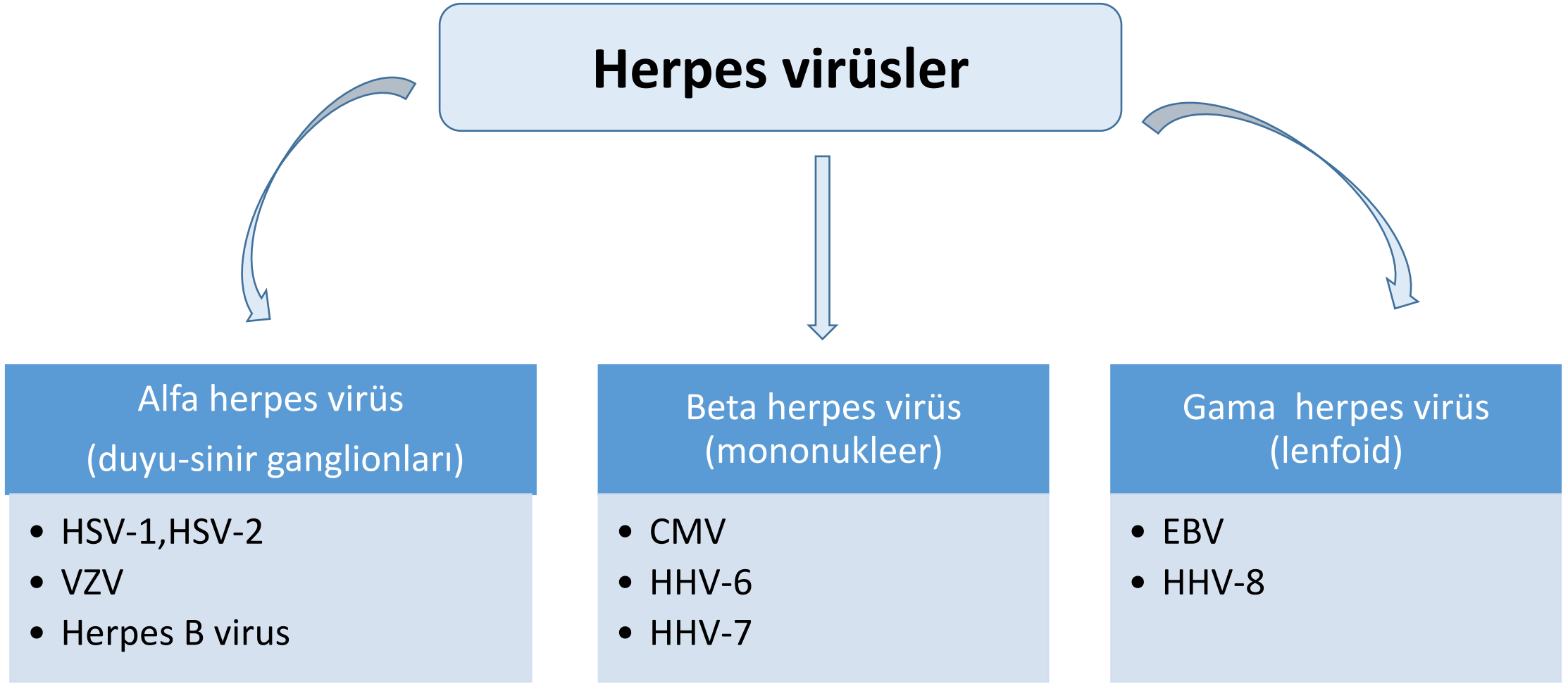
T.C. Sağlık Bakanlığı
Türkiye Kamu Hastaneleri Kurumu
SAĞLIK BİLİMLERİ ÜNİVERSİTESİ
İSTANBUL
FATİH SULTAN MEHMET
EĞİTİM VE ARAŞTIRMA HASTANESİ

Dirençli Herpes Viruslar İçin Eski ve Yeni Antiviraller

Doç. Derya Öztürk Engin
Fatih Sultan Mehmet Eğitim ve Araştırma Hastanesi
İnfeksiyon Hastalıkları ve Klinik Mikrobiyoloji Kliniği
30. Mart.2018



İnsanların %60-95'i herpes virüslerinden en az biri ile infekte olurlar

Yu-Chen Jiang et al. International Journal of Oral Science (2016) 8, 1–6.

Dirençli HSV infeksiyonlarında tedavi

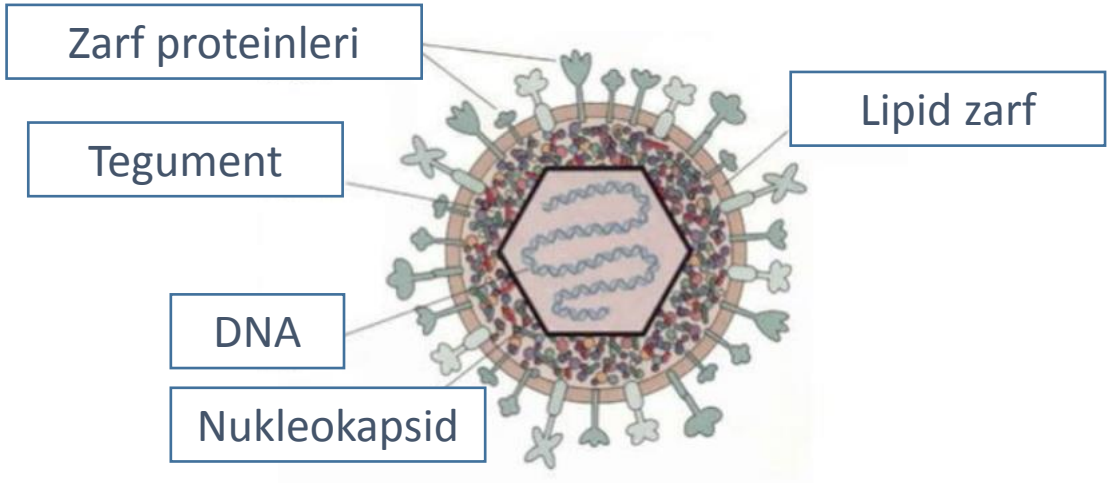


Table 1 Three classes of drugs approved for the treatment of HSV infections

Class of drugs	Licensed drugs
Acyclic guanosine analogues	Acyclovir, Ganciclovir, Penciclovir, Valaciclovir, Valganciclovir, Famciclovir
Acyclic nucleotide analogues	Cidofovir, Adefovir dipivoxil
Pyrophosphate analogues	Foscarnet

HSV, herpes simplex virus.

Yu-Chen Jiang et al. International Journal of Oral Science (2016) 8;1–6.

ASİKLOVİR

1982

- HSV genital infeksiyonu
- HSV ensefaliti
- HSV mukokta[illegible]oz inf[illegible]
- Zona[illegible]oster
- ➢ Bell [illegible]
- ➢ [illegible]
- ➢ H[illegible]
- [illegible]
- H[illegible]
- ➢ [illegible]asyon
- ➢ Vari[illegible]a
- ➢ Akut retinal nekroz
- ➢ VZV, HSV (organ nakli)
- ➢ Yaygın ekzema herpeticum
- ➢ HSV gingivostomatit

Gertrude Elion and George Hitchings, 1977 Nobel ödülü 1989

GANSİKLOVİR

1989

- CMV retiniti
- CMV profilaksi (organ nakli)
- ➢ CMV özefajiti, koliti, (HIV)
- ➢ CMV preemptif tedavi (HSCT)
- ➢ CMV hast. (organ nakli)
- ➢ CMV sekonder profilaksi
- ➢ CMV nörolojik tutulum
- ➢ Varisella-zoster retinal nekroz
- ➢ VZV, PORN, (HIV)

FOSKARNET

1991

- CMV retiniti
- Asiklovir dirençli HSV , immunsupresif hasta

✓ CMV özefajiti, koliti (HIV)
✓ CMV preemptif tedavi (HSCT)
✓ CMV profilaksi (HSCT)
✓ CMV nörolojik tutulum

FAMSİKLOVİR

1994

- Herpes zoster
- Genital herpes inf
- Genital herpes sup.
- Herpes labialis
- Tekrarlayan orolabial, genital HSV (HIV)

✓ Gental HSV; (HIV)
✓ HSV supresyon (HIV)
✓ Su çiçeği

VALASİKLOVİR

1995

- Herpes zoster
- HSV genital inf
- Genital HSV sup.
- Genital HSV sup. (HIV)
- Herpes labialis
- Su çiçeği

➢ Herpes B virüs profilaksi
➢ CMV reaktivasyonu, (HSCT)
➢ Genital HSV, (HIV)
➢ HSV keratit
➢ HSV orolabial, (HIV)
➢ HSV reaktivasyon, (HSCT)
➢ Herpes zoster, (HIV)
➢ Suçiçeği, (HIV)
➢ Akut retinal nekroz (HIV)
➢ VZV, profilaksi (HSCT)
➢ VZV reaktivasyon (HSCT)

SİDOFOVİR

1996

- CMV retiniti

✓ Asiklovir dirençli HSV

VALGANSİKLOVİR

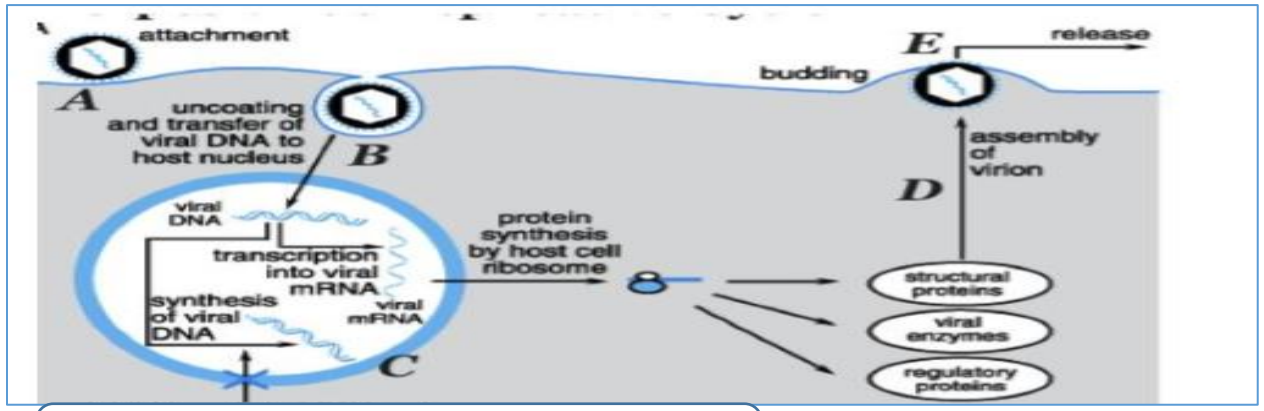
2001

- CMV profilaksis, organ naklinde
- CMV retiniti tedavi ve profilaksisi (HIV)

✓ CMV tedavi (organ nakli)
✓ CMV özefajit, kolit (HIV)
✓ CMV preemptif
✓ CMV sekonder profilaksi

Asiklovir

- Viral DNA polimerazı inhibe eder



Viral DNA polimeraz inhibitörü

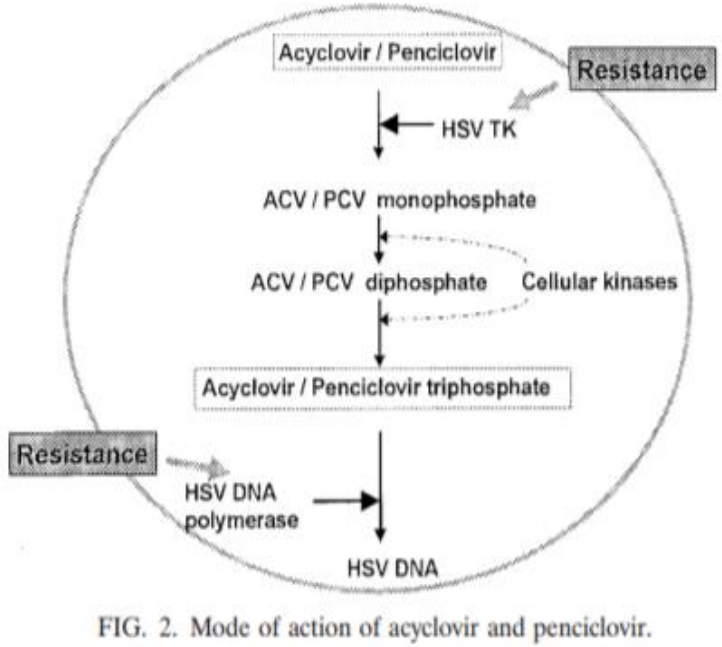


FIG. 2. Mode of action of acyclovir and penciclovir.

Yu-Chen Jiang et al. International Journal of Oral Science (2016) 8, 1–6.

Herpes virüslerin klinik örnekler için nüklezid/nükleotidlerin in vitro inhibitör konsantrasyonları

Virüs	Asiklovir	Pensiklovir	Gansiklovir	Sidofovir
HSV-1	0.02-1.9	0.2-1.8	0.05-0.6	0.4-3
HSV-2	0.3-2.9	0.3-2.4	0.05-0.6	0.4-3
VZV	0.8-5.2	0.9-5.1	0.2-2.8	0.25
CMV	2-57	52	0.2-2.8	0.2-0.9
EBV	1.6	-	1.5	<0.03
HHV-6	7-23	-	0.3-7	-
HHV-8	15-17	-	0.9-1.4	0.1-0.23

❖ Asiklovirin etkinliği, HSV-1 ve HSV-2 'de VZV den 10 kat fazla

- *Aoki FY*. *Antivirals against herpes viruses*. In: *Bennett* JE, Dolin R, Blaser MJ, editors. *Mandell*, *Douglas*, and *Bennett's principles* and *practice* of *infectious* diseases. 8th ed. Philadelphia: Saunders; 2015. p. 546–62.e7.

Asiklovir

Table 1. Characterization of acyclovir-resistant herpes simplex virus mutants.

Type of mutant	Thymidine phosphorylation (%)	Cross-resistance to penciclovir	Pathogenicity in mice (% relative to wild-type virus)		
			Neurovirulence after intracerebral inoculation	Replication at periphery	Ability to reactivate from latency
Wild type (none)	100	NA	100	100	100
TK-negative	<1	Yes	0.01–3	10–100	No (rare exceptions)
TK-partial	1–15	Yes (incomplete penetration)	3–100	20–100	10–100
TK-altered	Variable[a]	Variable	10	100	50–100
DNA polymerase	100	Variable	1–10	20–100	50–100

NOTE. Adapted from [30]. NA, not applicable; TK, thymidine kinase.
[a] Ability to phosphorylate thymidine depends on the nature of the mutation in the TK gene.

HSV Resistance in HIV Infection • CID 2004:39 (Suppl 5) • S249

İmmun sistemi baskılanmış bireylerde direnç oranı yüksek

- Uzun süreli tedaviler
- Konak direncindeki bozulma
- Virüs yükünün fazla olması, dirençli suşların baskın hale gelmesi

Piret J, Boivin G. Antimicrob Agents Chemother. 2011 Feb;55(2):459-72.
Chilukuri S et al. Dermatol Clin 2003; 21(2):311-20.

HSV infeksiyonlarında asiklovir direnç oranı

- İmmunitesi normal konakta % 0,1-% 0,7
- İmmunitesi baskılanmış bireyde % 4-27

Bacon TH, et al. Clin Microbiol Rev. 2003 Jan;16(1):114-28.
Kim JH, et al. Biol Blood Marrow Transplant. 2011 Feb;17(2):259-64.

- Dirençli olgularda infeksiyon daha şiddetli, daha yaygın, progresif seyirli ve daha fazla mukoza hasarı oluşur

Galdiero S, et al. J Pept Sci2013; 19(3): 148–158

Yüksek doz asiklovir ile tedavi

Yüksek doz, uzun süreli asiklovir tedavisi ile başarılı sonuç

Table 1. Summary of Case Reports

Case	Age, Sex	HCT Type*	GVHD	Immunosuppression		HSV Type; Location	MIC_{50} (μg/mL)†			Failed Treatment Regimens‡	Cont. ACV Dose mg/kg/day	Outcome, Time to Response
				PRED	Other		ACV	GCV	FOS			
1	37 F	TCD URD MA	Skin, GI Grade 2	<0.5 mg/kg/day	CsA	HSV-2; Genitalia Naris	10	30	22	ACV PO FAM PO ACV IV FOS i.v. CID i.v.	30	Resolved 6 weeks
2	47 F	URD MA	Skin Grade 4	<0.5-2 mg/kg/day	TAC MMF	HSV-2; Genitalia, buttocks, thighs	>48	45	>200	ACV i.v. FOS i.v.	45	Resolved 2 months
3	55 F	URD MA	Skin Grade 2	50 mg/day	TAC MMF	HSV-1; OP	>48	30	>48	ACV i.v. FOS i.v.	30	Resolved 1 week
4	44 F	URD MA	Skin Grade 4	60 mg/day	TAC	HSV-1; OP	>48	30-50	>48	ACV i.v. FAM PO	30-50	Partially resolved§
5	54 M	MRD MA	None	None	CSA ATG	HSV-1; Naris	>48	30	>100	ACV PO FAM PO	30	Resolved 1 week
6	52 M	MRD NMA	Skin Grade 4	1 mg/kg/day	TAC	HSV-1; OP	48	48	100	ACV i.v.	30	Resolved 1 week

Kim JH, et al. Biol Blood Marrow Transplant . 2011;17(2):259-64.

Asiklovir yan etki

- Halsizlik
- Baş ağrısı, hipotansiyon, kaşıntı, döküntü
- Bulantı-kusma
- Karaciğer fonksiyon testlerinde artma
- **Akut renal yetmezlik**
- Enjeksiyon alanında flebit

Asiklovirin yüksek serum konsantrasyonunda görülen nörotoksisite, özellikle BOS'taki 9-karboksimetoksimetilguanin (CMMG) ile ilişkili

Brady M et al. Clin Med (Lond). 2009;9(6):630.

Valasiklovir

- Valasiklovir asiklovire çevrilerek etki gösterir.
- Valasiklovirin, oral asiklovire göre biyoyararlanımı 3-5 kat daha fazla
- Valasiklovirde ilaç uyumu daha iyi
- Asiklovir direnci, yetersiz ilaç konsantrasyonu ile ilgili
- Valasiklovirin asiklovire göre daha yüksek kan düzeyi sağlaması nedeniyle immunosuprese hastanın başlangıç tedavisinde valasiklovir kullanılması direnç gelişmini önlemeye yardım edebilir

Chilukuri S et al. Dermatol Clin 2003; 21(2):311-20.

Famsiklovir

- Famsiklovirin aktif şekli pensiklovir
- Viral DNA polimeraz inhibitörü
- Pensiklovir dirençli HSV suşları, viral TK veya DNA polimerazda mutasyona sahip

Asiklovir dirençli HSV infeksiyonlarında genellikle etkisiz

Chilukuri S et al. Dermatol Clin 2003; 21(2):311-20.

Famsiklovir yan etki

- Baş ağrısı
- Bulantı-kusma
- İshal
- Kutanöz vaskülit

❖ Döküntü

❖ Halusinasyon, konfüzyon

❖ Lökopeni, nötropeni

Vidarabin (ara-A)

- Viral DNA sentezini inhibe eder
- İdoksuridin ve asiklovir dirençli suşlarda kullanılabilir
- Herpes simpleks ensefaliti, kronik EBV infeksiyonunda aktiviteye sahip

- Herpes ensefalitinde asiklovir, vidarabinden daha etkili
- 1992 yılında ABD'de kullanımdan kaldırılmış

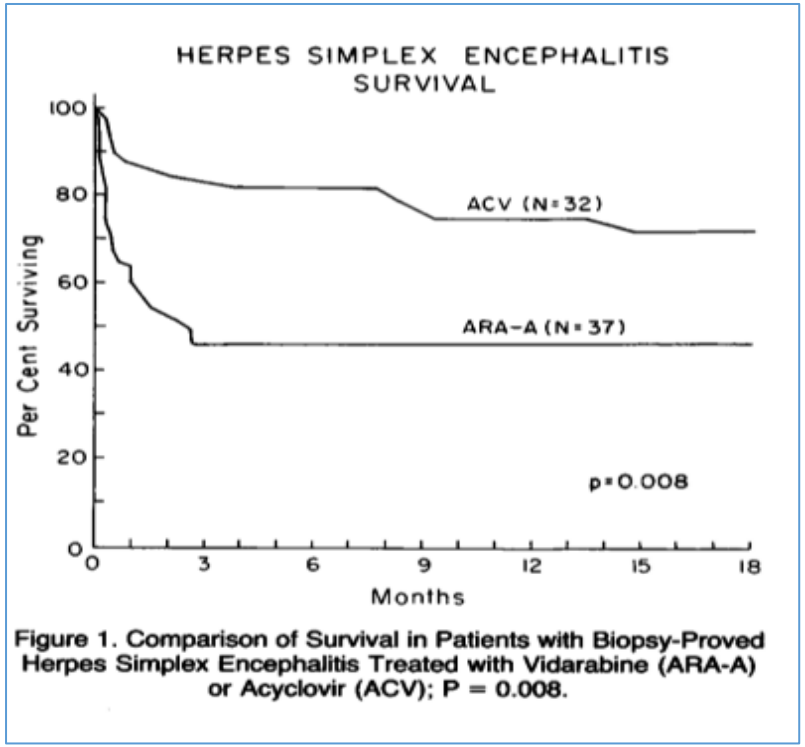


Figure 1. Comparison of Survival in Patients with Biopsy-Proved Herpes Simplex Encephalitis Treated with Vidarabine (ARA-A) or Acyclovir (ACV); P = 0.008.

Sköldenberg B et al. Lancet. 1984 Sep 29;2(8405):707-11.
Whitley RJ et al. N Eng J Med. 1986 Jan 16;314(3):144-9.

The NEW ENGLAND JOURNAL of MEDICINE

A CONTROLLED TRIAL COMPARING FOSCARNET WITH VIDARABINE FOR ACYCLOVIR-RESISTANT MUCOCUTANEOUS HERPES SIMPLEX IN THE ACQUIRED IMMUNODEFICIENCY SYNDROME

- Asiklovir dirençli mukokutanoz herpes infeksiyonunda foskarnet, vidarabinden daha etkili
- Daha az toksik

Safrin S, et al. N Engl J Med. 1991 22;325(8):551-5.

Brivudin

- Timidin nükleozid analoğu. HSV-1 ve VZV'ye etkili
- Viral DNA polimeraz inhibitörü
- Asiklovir ile çapraz direnç olabilir

1x125 mg 7 gün

Helikaz/primaz inhibitörleri

- Helikaz primaz kompleksi HSV DNA replikasyonu için gereklidir
- HSV tip 1 ve HSV tip 2'ye karşı etkili
- Replikasyonun inhibisyonu için timidin kinaz tarafından fosforilasyonu gerekmez
- TK eksikliği olan HSV de etkin

- ASP2151 (amenamevir)
- Bay 57-1293 (pritelivir)
- T157602
- BILS 22 BS

Amenamevir (ASP2151)

- HSV-1, HSV-2, VZV
- Nukleozid dirençli suşlara da etkili

Antiviral Res. 2017 Mar;139:95-101. doi: 10.1016/j.antiviral.2016.12.008. Epub 2016 Dec 24.

Profile of anti-herpetic action of ASP2151

Yajima M[1], Yamada H[1], Takemoto M[2], Daikoku T[2], Yoshida Y[1], Lor

Author information

İn vitro çalışmalarda amenavir, asiklovire göre daha iyi farmokokinetik profile sahip daha ekili

Abstract

The antiherpetic drugs acyclovir (ACV, valaciclovir) and penciclovir (famciclovir) are phosphorylated by viral thymidine kinase and terminate DNA synthesis. ASP2151 (amenamevir) and foscavir (PFA) directly inhibit viral helicase-primase and DNA polymerase, respectively, and inhibit replication of herpes simplex virus (HSV) and varicella-zoster virus. ACV, ASP2151, and PFA all inhibit HSV with a different mechanism of action and as a consequence, the kinetics of viral DNA accumulation and progeny virus production differ. This study focused on how viral DNA synthesis and its related events in the replication cycle would influence anti-HSV action of ACV, ASP2151, and PFA. ASP2151 suppressed HSV replication more efficiently than ACV at 10 × 50% effective concentration of plaque formation (EC_{50}), when treatments were started 0-24 h after infection. ASP2151 and PFA were more potent than ACV in suppressing viral DNA synthesis and infectious virus production when they were added up to 3 h following infection. The virus replicated in the presence of ACV was compared for the ratios of HSV DNA copy number to infectivity with that without ACV and infectivity of ACV-treated virus was less efficient than that without ACV-treatment. The EC_{50} of infected cells in the time course after infection was preserved in PFA, limited in ASP2151, and much increased for ACV, indicating that viral DNA synthesis had little effect on antiviral action of PFA and ASP2151 but reduced the susceptibility of ACV. ASP2151 showed a preferable profile as an anti-herpetic agent with a better pharmacokinetic profile than ACV.

JAPANESE DERMATOLOGICAL ASSOCIATION
THE JOURNAL OF DERMATOLOGY
doi: 10.1111/1346-8138.13948
Journal of Dermatology 2017; **44**: 1219–1227

ORIGINAL ARTICLE

Amenamevir, a novel helicase–primase inhibitor, for treatment of herpes zoster: A randomized, double-blind, valaciclovir-controlled phase 3 study

Makoto KAWASHIMA,[1] Osamu NEMOTO,[2] Mariko HONDA,[3] Daisuke WATANABE,[4] Juichiro NAKAYAMA,[5] Shinichi IMAFUKU,[6] Toshiyuki KATO,[7] Tsuneo KATSURAMAKI,[7] for the study investigators*

[1]*Department of Dermatology, Tokyo Women's Medical University, Tokyo,* [2]*Sapporo Skin Clinic, Sapporo,* [3]*Dr Mariko Skin and Dermatology Clinic, Yokohama,* [4]*Department of Dermatology, Aichi Medical University, Aichi,* [5]*General Medical Research Center,* [6]*Department of Dermatology, Fukuoka University Faculty of Medicine, Fukuoka,* [7]*Maruho Co., Ltd, Kyoto, Japan*

ABSTRACT

- **751 herpes zosterli hasta, çift kör randomize çalışma**
- **Döküntünün ilk 3 günü tedavi**
- **400 mg amenamevir /200 mg amenamevir/ valasiklovir 3x1000 mg**
- **Amenamevir 400 mg ve amenavir 200 mg tedavisi valasiklovir kadar etkili ve tolere edilir**

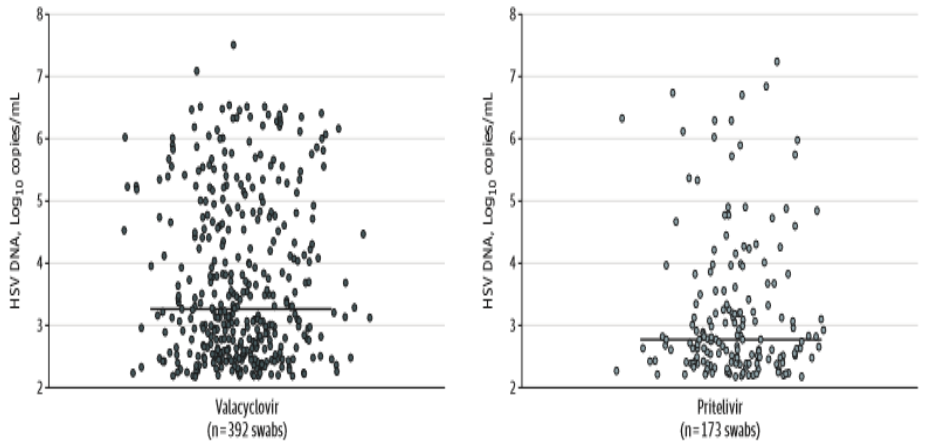
Pritelivir (AIC316)

Research

JAMA | Original Investigation

Effect of Pritelivir Compared With Valacyclovir on Genital HSV-2 Shedding in Patients With Frequent Recurrences
A Randomized Clinical Trial

Anna Wald, MD, MPH; Burkhard Timmler, MD; Amalia Magaret, PhD; Terri Warren, ANP; Stephen Tyring, MD, PhD; Christine Johnston, MD, MPH; Kenneth Fife, MD, PhD; Stacy Selke, MA; Meei-Li Huang, PhD; Hans-Peter Stobernack, PhD; Holger Zimmermann, PhD; Lawrence Corey, MD; Alexander Birkmann, PhD; Helga Ruebsamen-Schaeff, PhD



- Tekrarlayan genital HSV-2 hastalarında pritelivir ile valasiklovir karşılaştırılmış
- 28 günde HSV tespiti pritelivir kullanan hastalarda daha düşük

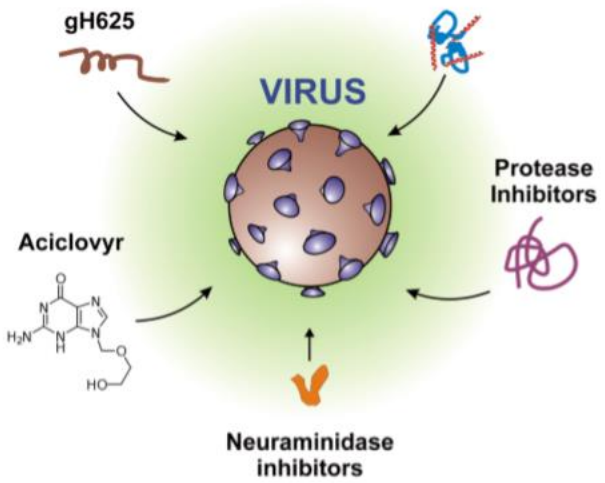
Yeni moleküller

- Flavonoids
- Sugar-containing compounds
- Peptides
- Notoginsenoside ST-4 inhibits
- Putranjivain A and pterocarnin A

Yu-Chen Jiang et al. International Journal of Oral Science (2016) 8, 1–6.

Peptide inhibitors against herpes simplex virus infections

Antimikrobiyal peptidler



Magainin
Dermaseptin

Melittin
Defensin (hBD-1)

Lactoferricin

Tachyplesin
Mytilin-A

Cathelicidin (LL-37)
Brevinin-1
Indolicidin
Cecropin

Penaeidin-3a

Galdiero S, et al. J Pept Sci 2013; 19(3): 148–158.

Ribonukleotid reduktaz inhibitörleri (BILD 1633 SE)

- Ribonukleotid reduktaz, ribonukleotidten deoksiribonukletid oluşumunu katalize eder, latent formdan reaktivasyona geçiş için gerekli
- Fare deneylerinde HSV keratitinde etkili olduğu bildirilmiş

Piret J, Boivin G. Antimicrob Agents Chemother. 2011 Feb;55(2):459-72.

Topikal tedaviler

- Asiklovir
- Pensiklovir
- Vidarabin

- Trifluridin
- İmuquimod
- İdoksurdin
- Dococanol

Contents lists available at ScienceDirect

Journal of Clinical Virology

journal homepage: www.elsevier.com/locate/jcv

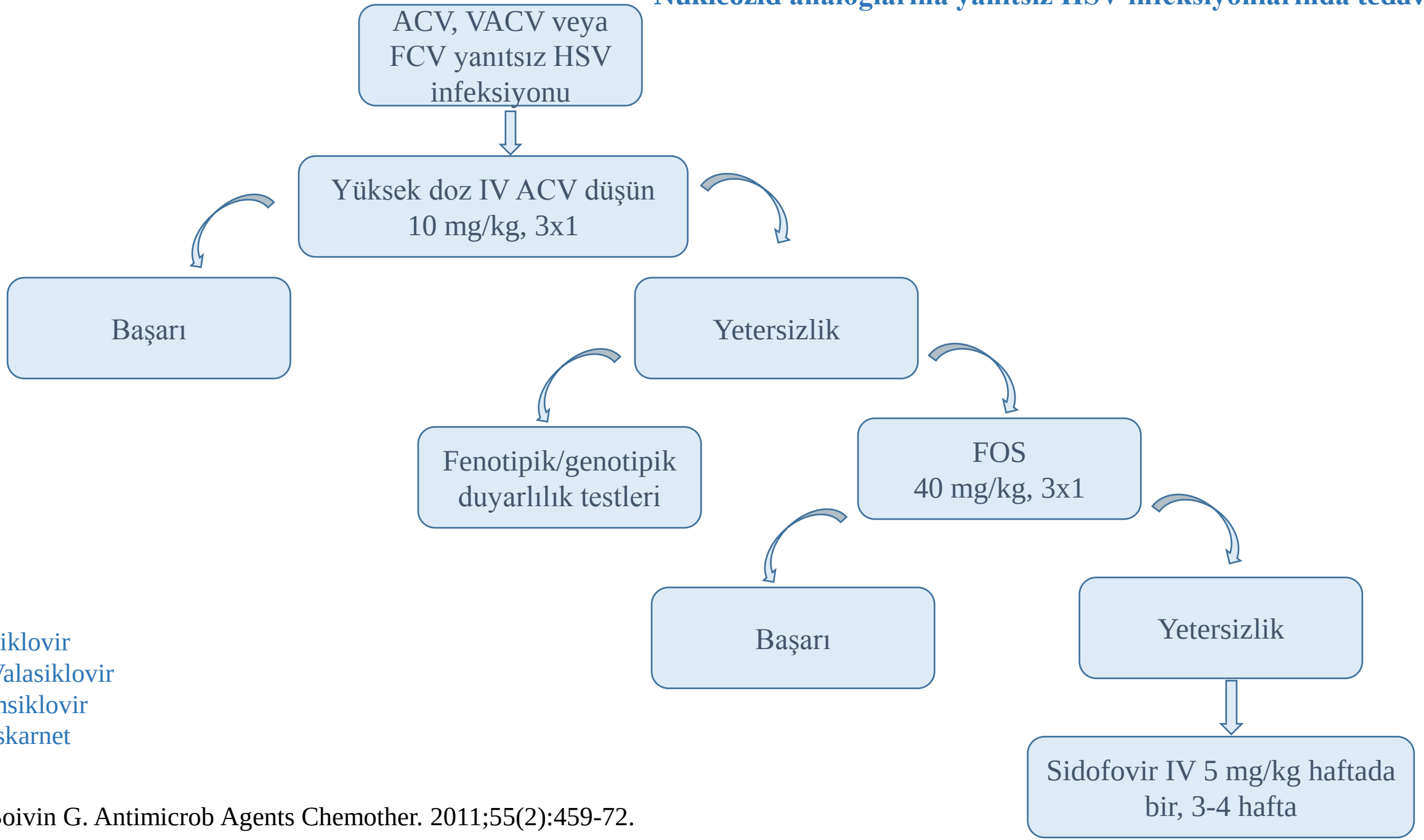
Case Report

Acyclovir-resistant herpes simplex encephalitis in a patient treated with anti-tumor necrosis factor-α monoclonal antibodies

Kinda Schepers[a], Antonio Hernandez[b], Graciela Andrei[c], Sarah Gillemot[c], Pierre Fiten[d], Ghislain Opdenakker[d], Jean-Christophe Bier[b], Philippe David[e], Marie-Luce Delforge[f], Frédérique Jacobs[a], Robert Snoeck[c,*]

- Adalimumab kullanan bir hastada gelişen, asiklovir dirençli HSV ensefaliti
- Asiklovir ve foskarnet ile başarılı sonuç

Nukleozid analoglarına yanıtsız HSV infeksiyonlarında tedavi



ACV: Asiklovir
VACV: Valasiklovir
FCV:Famsiklovir
FOS: Foskarnet

Piret J, Boivin G. Antimicrob Agents Chemother. 2011;55(2):459-72.

2017 European guidelines for the management of genital herpes

İmmunosuprese hasta, asiklovir dirençli HSV şüphesi
(Daha önce asiklovir dirençli HSV varsa veya standart anti-viral tedavide yetersizlik varsa)

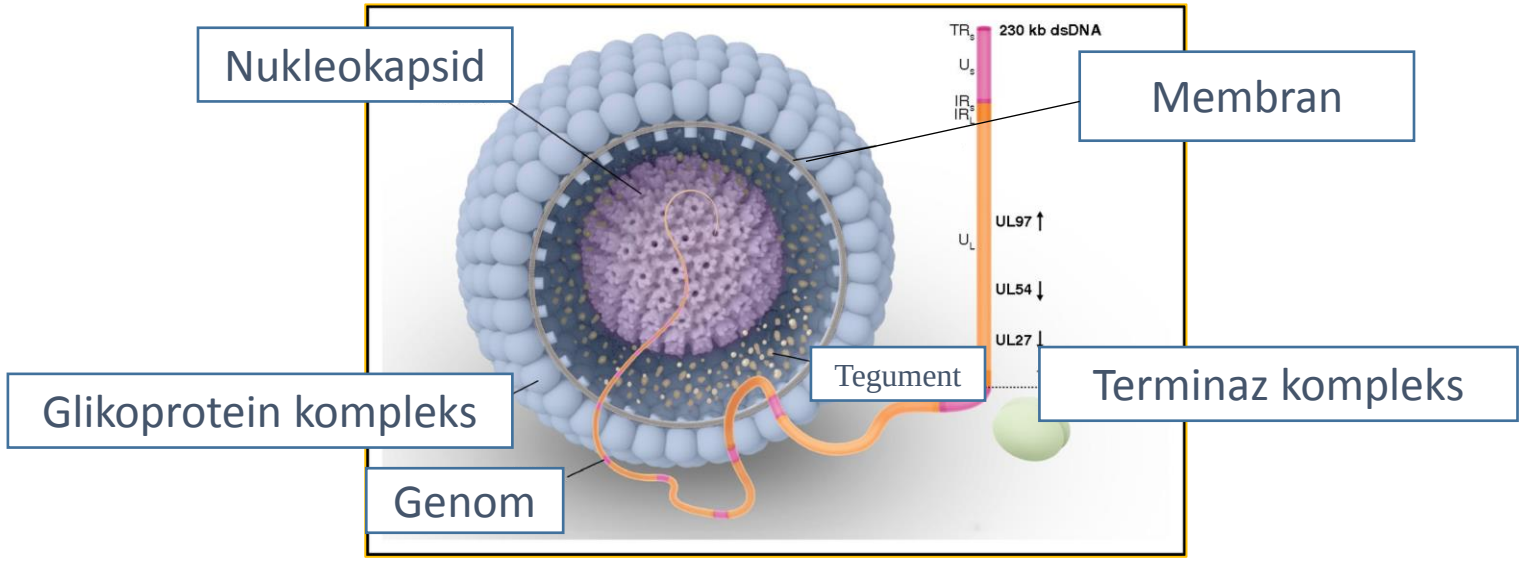
Kültür veya PCR

3-5 günlük tedaviden sonra hala yeni lezyon ortaya çıkıyorsa,
Asiklovir 5x800 mg/valasiklovir 2x1 g/famsiklovir 2x750 mg

Şiddetli olmayan lezyonlarda
Foscarnet %1 krem veya
Sidofovir %1 jel
Trifluridin 3x1 lezyonlar iyleşene kadar tekbaşına veya interferon alfa ile kombine veya imiquimod krem

Şiddetli lezyonlarda
Foskarnet 40 mg/kg 3x1 veya
Sidofovir 5 mg/kg haftada bir+probenesid
Sistemik tedavi klinik düzelme olana kadar sürdürülmeli

Dirençli CMV infeksiyonlarında tedavi



Gansiklovir

- Viral DNA sentez inhibitörü
- CMV infekte hücrelerde, infekte olmayan hücrelere göre konsantrasyon 10 kat yüksek

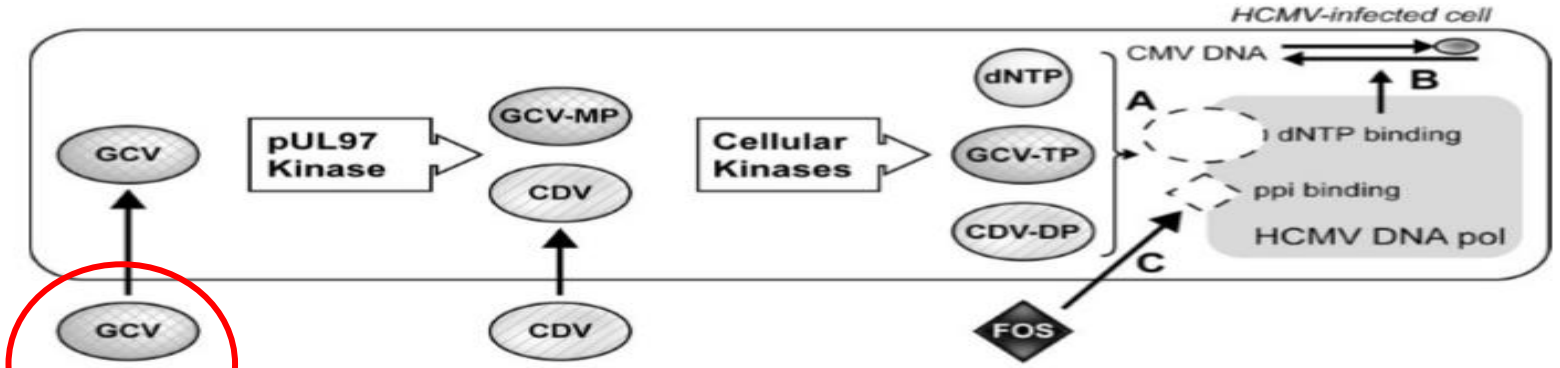


FIG. 1. Mechanisms of action of systemic antivirals approved for treatment of CMV infections. GCV and CDV, once phosphorylated, compete with dNTPs for the binding site on the DNA *pol* (A) and are incorporated into HCMV DNA (B), thus inhibiting viral DNA replication. FOS directly inhibits viral DNA replication by blocking the pyrophosphate (ppi) binding site (C), thus preventing ppi cleavage from incoming dNTPs and subsequent incorporation of the nucleotide into viral DNA. MP, DP, and TP, monophosphate, diphosphate, and triphosphate, respectively.

Gilber C et al. Antimicrob Agents Chemother. 2005 Mar;49(3):873-83.

Gansiklovir direnci

- Akciğer nakillerinde gansiklovir direnci %3.6-9
- Böbrek- pankreas alıcılarında %21
- Böbrek alıcısında %5

Gilbert C et al. Antimicrob Agents Chemother 2005 Mar; 49(3): 873–883.

Direnç için risk

- Uzun süreli anti-viral ilaç maruziyeti
- Yetersiz düzeyde ilaç kullanımı
- Yoğun immunosupresyon
- D+/ R-

Kotton CN, et al. Transplantation 2013 Aug 27;96(4):333-60.

Şiddetli olmayan, foskarnet kullanılamayan olgularda yüksek doz gansiklovir/valgansiklovir kullanılabilir

CLINICAL AND TRANSLATIONAL RESEARCH

Use of High-Dose Ganciclovir for the Treatment of Cytomegalovirus Replication in Solid Organ Transplant Patients With Ganciclovir Resistance-Inducing Mutations

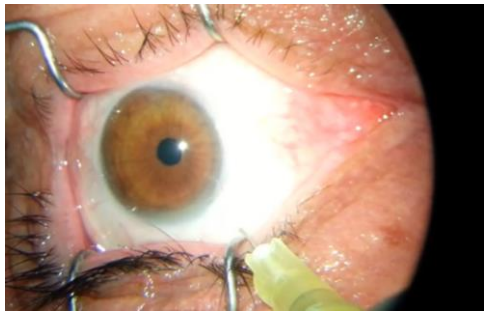
Irene Gracia-Ahufinger,[1] Juan Gutiérrez-Aroca,[1] Elisa Cordero,[2] Elisa Vidal,[3] Sara Cantisán,[4] Domingo del Castillo,[5] Cecilia Martín-Gandul,[6] Antonio Rivero,[3] and Julián Torre-Cisneros[3,7]

Background. Experience with high-dose ganciclovir for the management of resistant cytomegalovirus (CMV) replication in transplant patients is limited despite its adoption as an effective therapy by some consensus documents. **Methods.** We studied six cases of CMV replication in solid organ transplant patients whose genotypic testing showed mutations associated with different levels of resistance to ganciclovir. All were treated with high-dose intravenous ganciclovir (7.5–10 mg/kg/12 hr) or oral valganciclovir (1350–1800 mg/12 hr) corrected according to creatinine clearance. The virologic response was considered positive if the CMV plasma viral load was undetectable. Safety was evaluated by clinical assessment, including the review of vital signs and laboratory tests.

Gansiklovir/Yan etki

IV uygulama

- Nötropeni (%24-40)
- Trombositopeni (%15-20)
- Baş ağrısı, davranış değişiklikleri, konfuzyon, psikoz, koma
- İV infuzyonla ilişkili komplikasyonlar
- Döküntü, ateş, bulantı-kusma
- Anemi, karaciğer testlerinde artış
- Nefrotoksisite (nefrotoksik ilaçlarla birlikte verildiğinde risk artar)



İntravitreal uygulama

- ❖ Görme kaybı
- ❖ Kanama
- ❖ İnfeksiyon
- ❖ Retinal ayrılma

Valgansiklovir

- Gansiklovirin valin esteri
- İnsan barsak mukozasında valin esteraz, valin esteri parçalar, gansiklovir olarak kana girer
- Oral biyoyararlanımı gansiklovire göre daha yüksek (%6-8; %68)

Foskarnet

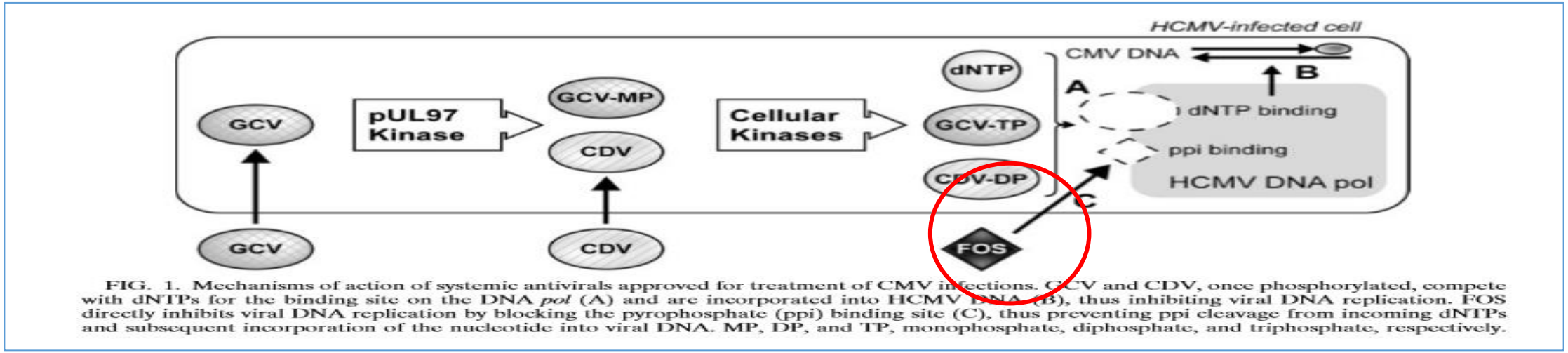


FIG. 1. Mechanisms of action of systemic antivirals approved for treatment of CMV infections. GCV and CDV, once phosphorylated, compete with dNTPs for the binding site on the DNA *pol* (A) and are incorporated into HCMV DNA (B), thus inhibiting viral DNA replication. FOS directly inhibits viral DNA replication by blocking the pyrophosphate (ppi) binding site (C), thus preventing ppi cleavage from incoming dNTPs and subsequent incorporation of the nucleotide into viral DNA. MP, DP, and TP, monophosphate, diphosphate, and triphosphate, respectively.

Gilbert C et al. Antimicrob Agents Chemother. 2005 Mar;49(3):873-83.

- İnorganik pirofosfat analoğu
- Herpes virüslerinde DNA polimerazı inhibe eder

Foskarnet

İmmunosuprese hastalarda CMV retiniti /
Asiklovir dirençli mukokutanoz HSV infeksiyonları

- Gansiklovir dirençli CMV, asiklovir dirençli HSV ve VZV suşlarına ekili

❖ UL97 mutasyonundan dolayı gansiklovire dirençli suşlar foskarnet ve sidofovire duyarlı

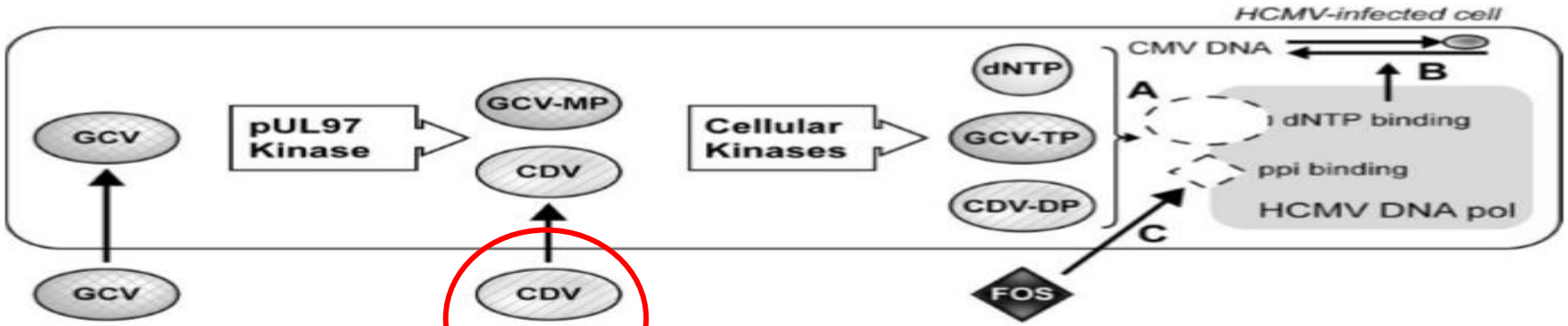
Schreiber A et al. Expert Opin Pharmacother 2009;10(2):191-209.

Foskarnet/yan etki

- Nefrotoksisite (1/3 olguda)
- Hipokalsemi
- Hipomagnazemi
- Hipofosfatemi/hiperfosfatemi
- Hemorajik sistit, genital ülser

- ❖ Akut distoni, baş ağrısı, nöbet
- ❖ Tremor, halüsinasyon
- ❖ Ateş, döküntü, ishal
- ❖ Bulantı-kusma
- ❖ Anemi, granulositopeni
- ❖ Kalp bloğu, EKG değişikliği

Sidofovir



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Gilbert C, et al. Antimicrob Agents Chemother. 2005;49(3):873-83.

Viral DNA sentez inhibitörü, nükleotid analogu

- HSV, CMV, EBV
- HHV-6, HHV-7, HHV-8
- Papillamavirus, polyomavirus, pox virüs, adenovirüse karşı etkili

Sidofovir

- TK-eksikliği olan, TK dirençli, TK-değişikliği olan, asiklovir dirençli HSV virüslerine etkili
- UL-97 mutasyonu nedeniyle gansiklovir dirençli CMV suşlarına etkili
- UL-54 mutasyonu olan suşlara etkisiz

Haftada bir kez 5 mg/kg kullanılır

Sidofovir/yan etki

- Dozla ilişkili renal yetmezlik
- Başka nefrotoksik ilaç alanlarda kontrendike
- **Anlamlı proteinuri (2+) veya kreatinin klerensi 55 mL/dak altındaysa nispi kontrendike**
- Birlikte probenesid uygulanması ve hidrasyon sonrası sidofovir uygulanması önerilir

- Nötropeni
- Bulantı, kusma, diyare
- Baş ağrısı, döküntü, iritis, üveitis

EK TEDAVİ YAKLAŞIMLARI

CMV Immunglobulini

- Opsonizasyon ve fagositoz ile CMV partiküllerini dolaşımdan temizler
- Hücre içerisine CMV girişini azaltır

Yaşamı tehdit eden CMV hastalığı, özellikle şiddetli pnömoni tablosunda ek tedavi olarak kullanılabilir

Torre-Cisneros J, et al.Transplant Rev (Orlando). 2016 Jul;30(3):119-43.

CMV Immunglobulini

Akciğer transplantasyonlu hastada CMV infeksiyonu

- Gansiklovir tedavisine yanıtsız.
- Sidofovir+ CMV IgG ile başarılı tedavi

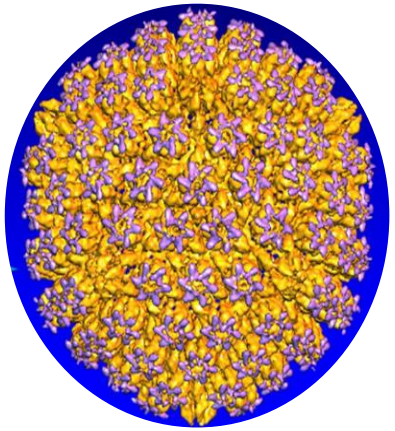
Wilkens H et al. Case Rep Transplant. 2016;2016:4560745.

Kemik iliği nakli sonrası CMV pnömonisi

Gansiklovir ve yüksek doz intravenöz immunglobulin ile başarılı tedavi

Emanuel D et al. Ann Intern Med 1988;109(10):777-82.

Leflunomide

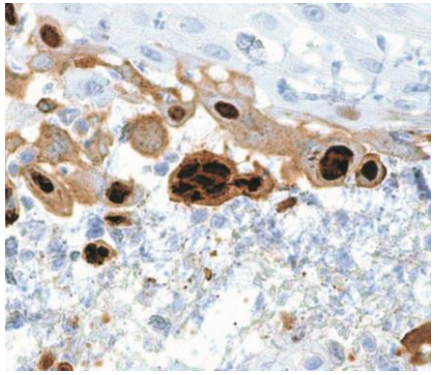


- İmmunosupresif ilaç, romatoid artrit, psöriatik artrit, solid organ nakillerinin reddinde kullanılır
- 1994 yılında viral kapsit birleşmesini inhibe ettiği gösterilmiş
- Dirençli CMV infeksiyonununda kullanılmış
- Gansiklovir dirençli CMV de başarı oranı %66.7

Waldman WJ et al. Transplantaion 1999 Sep 27;68(6):814-25
Avery RK et al. Bone Marrow Transplant. 2004 Dec;34(12):1071-5.
Morita S et al. J Clin Virol. 2016 Sep;82:133-138.
Roger MR et al. Case Rep Infect Dis2017;2017:1589356.

Leflunomide

- 2001 yılında HSV'ye karşı da etkili olduğu gösterilmiş.
- Psödotümoral görünümlü tedaviye yanıtsız genital HSV olgularında kullanılmış
- Uzun süreli tedavide yan etki görülmemiş



Roger MR et al. Case Rep Infect Dis.2017:1589356.

The Antiviral Activities of Artemisinin and Artesunate

Thomas Efferth,[1] Marta R. Romero,[3,5] Dana G. Wolf,[4] Thomas Stamminger,[2] Jose J. G. Mar and Manfred Marschall[2]

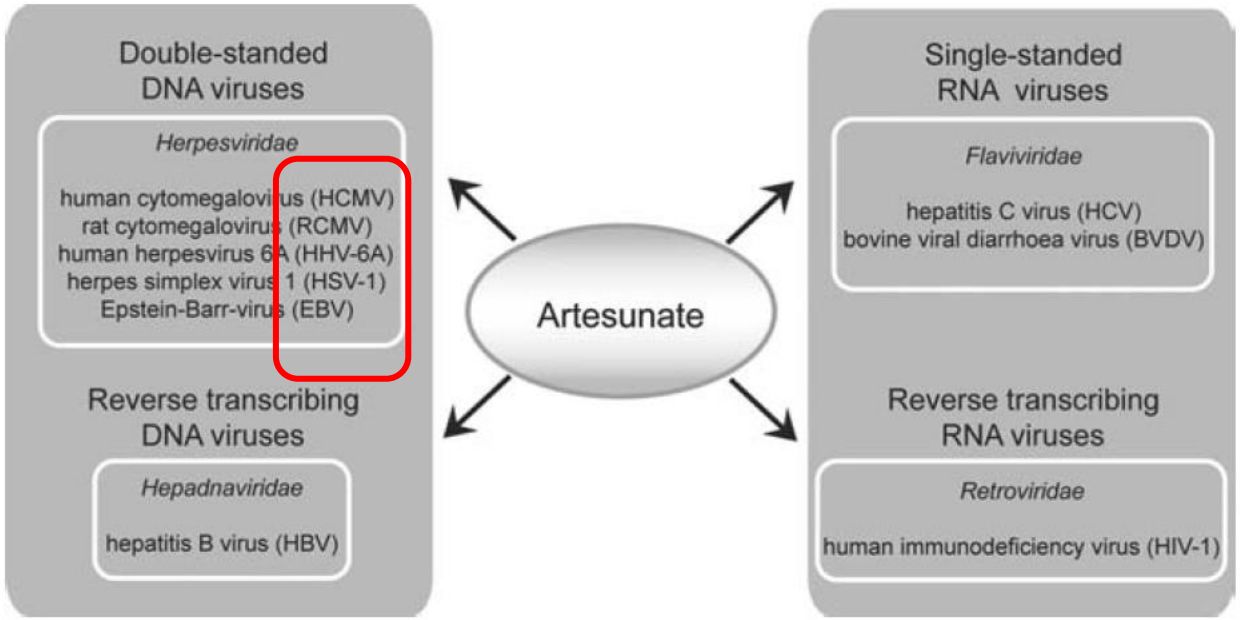


Figure 3. Spectrum of antiviral activity of artesunate

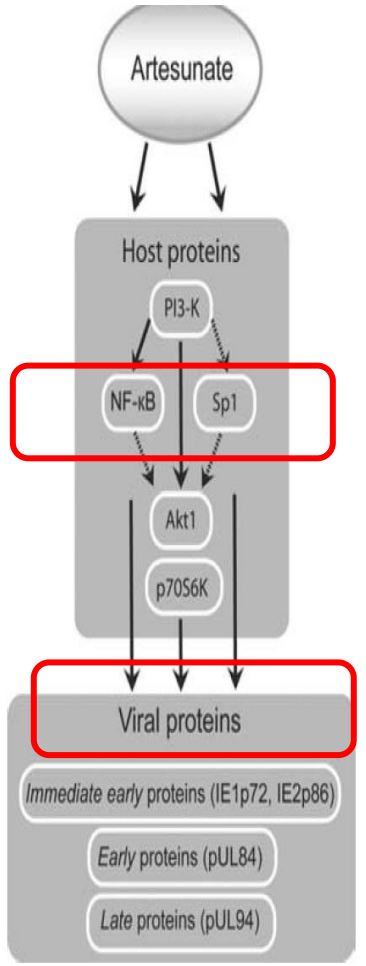


Figure 2. Hypothetical molecular mechanism of artesunate against human cytomegalovirus.

Efferth T et al. Clin Infect Dis.2008 Sep 15;47(6):804-11.

- Kemik iliği nakli sonrası gelişen CMV infeksiyonu
- Foskarnet, sidofovire yanıtsız
- Artesunat ile düzelen olgu sunumları

Shapira MY, et al. Clin Infect Dis 2008; 46: 1455–7.
Sellar RS, et al. Bone Marrow Transplant. 2012 Nov;47(11):1482-3.

- Leflunamide ve artesunate ile ilgili sonuçlar yetersiz ve çelişkili
- Alternatif tedavi yokluğunda kullanılması düşünülmeli

Torre-Cisneros J, et al. Transplant Rev (Orlando). 2016 Jul;30(3):119-43.

	Letermovir	Brincidofovir	Maribavir
Dose	80 mg daily oral	200 mg orally once weekly OR 100 mg twice weekly	400 daily or 400 bid [*]
Compound information	Novel class of low-molecular-weight compounds, 3,4 dihydro-quinazolines	Lipid antiviral conjugate comprised of a lipid (1-0-hexadecyl-oxypropyl) covalently linked to the acyclic nucleotide analogue cidofovir	Benzimidazole nucleoside
Mechanisms of action	Terminase inhibitor: blocks viral replication without inhibiting the synthesis of progeny CMV DNA or viral proteins	Remains intact in plasma and deliver drug directly to the target cell resulting in enhanced cellular uptake and high intracellular levels of cidofovir (CDV) diphosphate which competitively inhibits the incorporation of deoxycytidine triphosphate into viral DNA by viral DNA polymerase. This disrupts further chain elongation [55]	Inhibition of viral encapsidation and nuclear egress of viral particles from infected cells
Toxicities	None reported	Mild side effects include abdominal pain or discomfort, and aphthous stomatitis [38]	Taste disturbance, Skin rash [56]
Viral gene targets	Viral pUL56 subunit	Viral DNA polymerase	Viral pUL97 kinase

[*] Maribavir 100 mg bid did not have sufficient anti-CMV activity in liver transplant patients. 400 mg daily and 400 mg bid have been shown to be safe but anti-CMV activity is not clear.

Verghese PS et al. Drugs Future 2013 May;38(5):291-298.

- Maribavir, UL97 kinaz inhibitörü olması nedeniyle gansiklovirin etkinliğini in vitro inhibe eder

Table 9
Setting for new drugs against CMV.

Drug	Prophylaxis	Preemptive therapy	Treatment of CMV-resistant disease
Brincidofovir [259,319]	Lower incidence of CMV disease or high-level viremia in HSCT at a dose of 100 mg twice weekly compared to placebo		Successful in 4 out of 5 KT at a dose of 100 or 200 mg twice weekly
Letermovir [260,261,320]	Lower CMV reactivation in HSCT at a dose of 120 or 240 mg qid for 12 weeks after engraftment compared to placebo	Viral clearance was achieved in 50% of KT with active CMV replication at a dose of 40 mg bid or 80 mg qid for 14 days compared to 26% in the standard of care	One report of success at a daily dose of 240 mg during 49 days for CMV disseminated disease in LT
Maribavir [82,83,258,321]	Failed to show non-inferiority to ganciclovir for CMV disease in OLT at a dose of 100 mg bid for 14 days		Successful in 4 out of 7 SOT at a daily dose higher than 800 mg. One report of proven maribavir resistance when treating a high initial CMV viral load

CMV: cytomegalovirus; HSCT: hematopoietic stem cell transplantation; OLT: orthotropic liver transplantation; KT: kidney transplantation; LT: lung transplantation; SOT: solid organ transplantation.

Table 6. New anti-CMV antivirals

Drug	Mechanism of action	Route	Spectrum	Prophylactic studies in allogeneic SCT	
				Phase II	Phase III
Maribavir	UL 97 inhibition	ORAL	CMV and EBV	Winston DJ, 2008 (98): 111 patients Primary end-point: Success Failures: 7% vs. 46% placebo	Marty FM, 2011 (4): 681 patients Primary end-point: Failure
Brincidofovir	Viral DNA polymerase inhibition (UL 54)	Oral	The broadest (CMV, EBV, adenovirus,...)	Marty FM, 2013 (5): 230 patients Primary end-point: Success Failures: 10% vs. 37% placebo	Marty FM, 2016 (99): 458 patients Primary- end-point: Failure
Letermovir	CMV terminase complex inhibition (UL 56)	Oral & iv	CMV	Chemaly RF, 2014 (6): 132 patients Primary end-point: Success Failures: 29% vs. 64% placebo	Ongoing

de la Cámara R. Mediterr J Hematol Infect Dis. 2016 20;8(1):e2016031

T hücreli immunoterapi

- Yeterli immun cevap gelişmeyen ve tedaviye dirençli şiddetli CMV hastalığı için solid organ transplantasyonlu hastalarda kullanılabilir.
- Ancak klinik tecrübe sınırlı

Torre-Cisneros J, et al.Transplant Rev (Orlando). 2016 Jul;30(3):119-43.

Table 1. Main characteristics of the patients included in the cohort according to the maintenance immun
regimen administered.

	mTOR inhibitors *n* = 95	Calcineurin inhib	
Mean age (SD)	56.9 (13.5)	51	
Male gender (%)	62 (65%)		
Aetiology of CRF			
Diabetes	7 (7%)		
Glomerular	7 (7%)		
Nephroangiosclerosis	15 (16%)		
Tubulointerstitial	4 (4%)		
Polycystic disease	12 (1		
Other			
Unknown		4%)	
Retransplantation		(24%)	0.009
Type of kidney transplantation			<0.001
Living donor		132 (52%)	
Deceased donor – heart beating		108 (42%)	
Deceased donor – nonheart beating		15 (6%)	
Donor/Recipient CMV serology			0.001
D+/R+		184 (72%)	
D+/R−	3%)	21 (8%)	
D−/R+	(9%)	41 (16%)	
D−/R−	4 (4%)	9 (4%)	
High-intensity i	76 (80%)	165 (65%)	0.006
Acute reject	9 (10%)	48 (19%)	0.035
Anti-CM	53 (56%)	170 (67%)	0.060
Graf	4 (4%)	6 (2%)	0.469
	5 (5%)	9 (4%)	0.540
	al) (median, IQR) 1.57 (1.15–1.89)	1.29 (1.04–1.58)	0.005
	tion 7 (7%)	16 (6%)	0.713
	12 (13%)	23 (9%)	0.317

SD, viation; CRF, chronic renal failure; IQR, interquartile range.

- 350 renal transplant hastası
- M-TOR inibitörü (%27) içeren immunosupresyon ve kalsinörin (%73) inhibitörü içeren immunosüpresyon
- M-TOR inhibitörü alanlarda CMV infeksiyonu düşük

Carlos C., et al. Transplant International 2016; 29: 1216–1225

- Solid organ transplantasyon hastalarında tekrarlayan veya gansiklovir dirençli CMV hastaları için kalsinörin inhibitörlerinin M-TOR inhibitörleri ile değiştirilmesi önerilir

Torre-Cisneros J, et al. Transplant Rev (Orlando). 2016 Jul;30(3):119-43.

Fomivirsen

- HIV infekte hastalarda CMV retinitinin erken döneminde kullanılır
- İntravitreal uygulanır
- 330 μg 2 haftada bir, 2 hafta; devamı 4 haftada bir

- Fomivirsen, korneal ülsere neden olabilir (tedavisi topikal steroid)

Schreiber A et al. Expert Opin Pharmacother 2009 Feb;10(2):191-209.

cyclopropravir

AAC
Journals.ASM.org

Metabolism of Cyclopropavir and Ganciclovir in Human Cytomegalovirus-Infected Cells

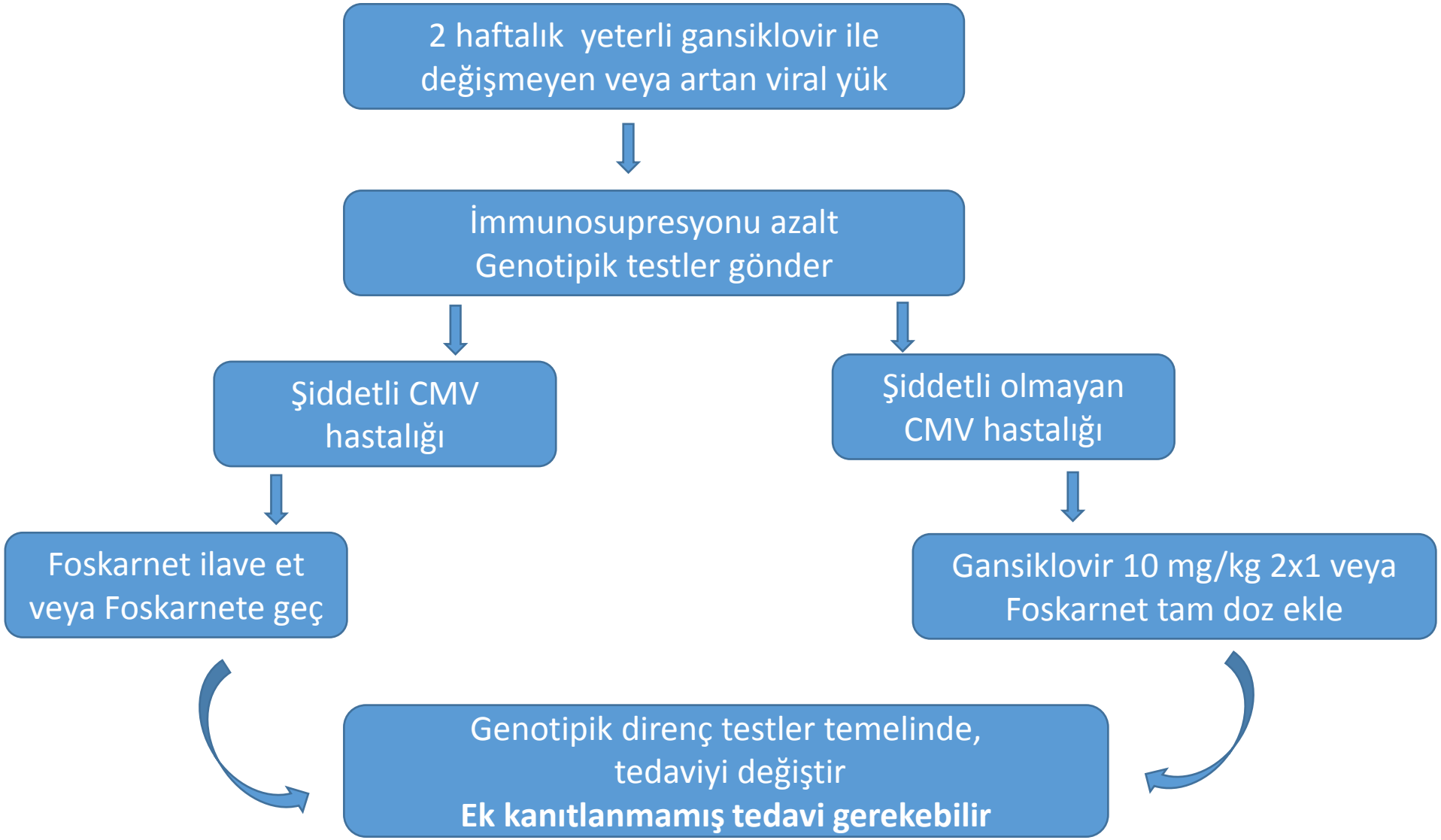
Brian G. Gentry,[a] John C. Drach[b]

Department of Pharmaceutical, Biomedic… Moines, Iowa, USA[a]; Department of Biologic and Materials Sciences, Schoo…

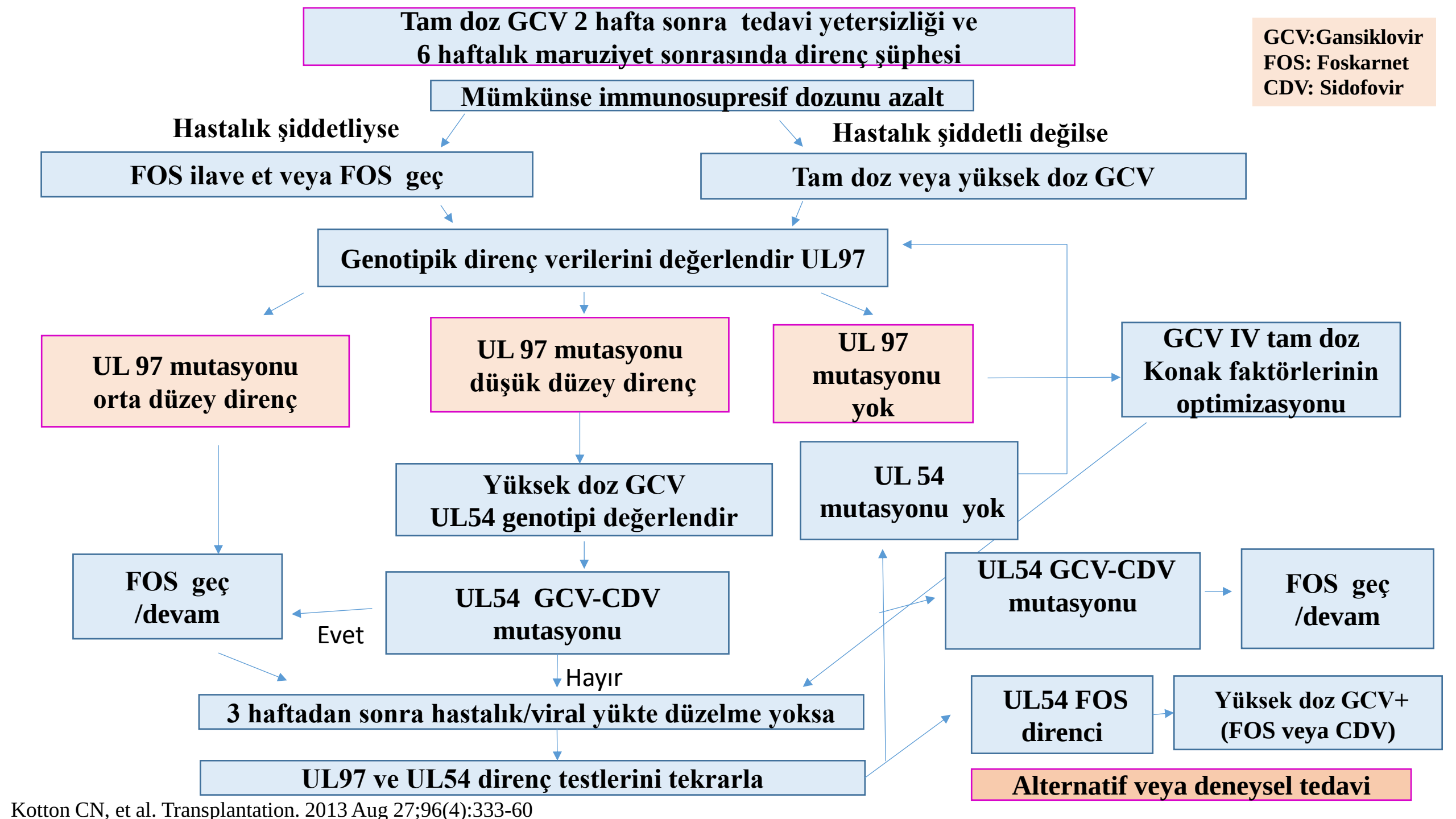
Human cytomegalovirus (HCM… ically immature and immunocompromised patients. T… anciclovir (GCV). However, high incidence rates of ad… PV) is 10-fold more effective against HCMV *in vitro* t… ctively) without any observed increase in cytotoxici… llen, Y. C. Cheng, and J.

- DNA polimeraz inhibitörü
- Anti-CMV aktivitesi var
- İn vitro gansiklovirden 10 kat daha etkili

Gansiklovir direnci



Razonable RR et al. Am J Transplant. 2013; 13: 93–106



Kotton CN, et al. Transplantation. 2013 Aug 27;96(4):333-60

Şiddetli olmayan CMV hastalığı Foskarnet verilemeyen UL97 mutasyonu yüksek düzey direnç yoksa	→	Gansiklovir 10 mg/kg , 2x1
UL97 de mutasyonu gansiklovir için yüksek düzey direnç veya UL 54 mutasyonu varsa	→	Foskarnet
Şiddetli CMV hastalığı Şiddetli immunosupresyonu olan D+/R-	→	Foskarnet veya Foskarnet+ Gansiklovir 10 mg/kg , 2x1

UL54 gen mutasyonu ekarte edilmedikçe, klinik şiddetli değilse sidofovir önerilmez

Torre-Cisneros J, et al. Transplant Rev (Orlando). 2016 Jul;30(3):119-43.

TABLE 3 Ganciclovir-resistant CMV infections, treatment regimens and outcomes[a]

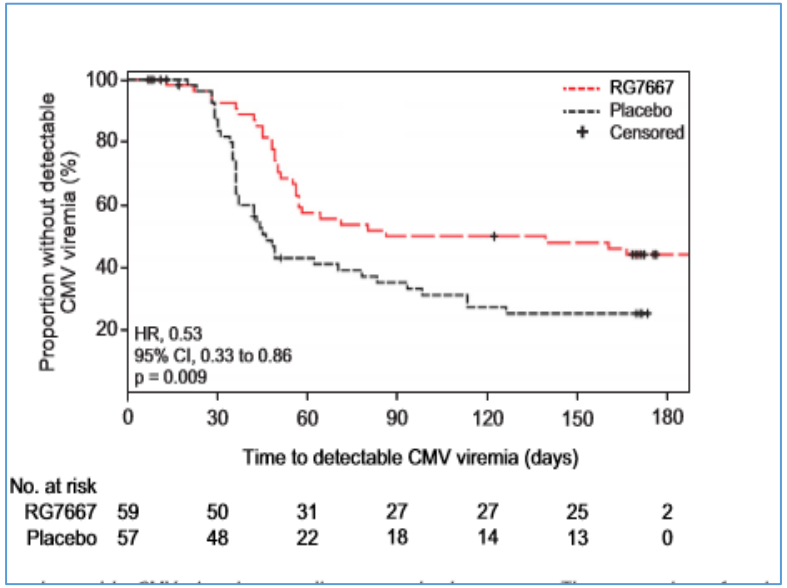
Patient no.	Mutation(s) (drug resistance)	Type of infection (serum $\log_{10}$ viral load)	Cylex (ng/ml ATP)	Treatment regimen	Viral load response	Decay half-life (days)	Subsequent course	Follow-up (mo)	Outcome classification
Treatment with foscarnet-containing regimens									
1	UL97 C603W (GCV)	Viremia (3.60 log)	634	FOS, GCV, CMV Ig	Suppressed (34 days)	3.5	Maintained on FOS until death (120 days; not CMV related)	4	Suppressed on FOS
2	UL97 H520Q (GCV)	Pneumonitis (3.01 log)	138	FOS, CMV Ig	Suppressed (14 days)	1.8	Relapsed on CMV Ig + LEF maintenance. Retreated with FOS. Retransplanted due to allograft failure.	30	Relapse
3	UL97 M460V (GCV)	Viremia (2.54 log)	115	FOS, CMV Ig	Suppressed (15 days)	2.1	Relapsed with pneumonitis, then ongoing viremia despite FOS + CMV Ig,+LEF + RAP	17	Relapse
5	UL97 M460V (GCV)	Pneumonitis and bronchial polyp (4.41 log)	397	FOS, CMV Ig	Suppressed (27 days)	2.6	Relapsed on CMV Ig + RAP maintenance	8	Relapse
7	UL97 M460V (GCV)	Pneumonitis (4.88 log)	76	FOS	Not suppressed	NA	Died of pneumonitis (28 days)	NA	Failure
8	UL97 L595S (GCV)	Viremia (4.88 log)	87	FOS, GCV, LEF	Not suppressed	NA	Died of pneumonitis (153 days)	NA	Failure
9	UL97 603W/C (GCV)	Pneumonitis (4.21 log)	341	FOS, CMV Ig	Suppressed (35 days)	3.4	Died of pneumonitis (40 days)	NA	Failure
10	UL97 A594P (GCV)	Pneumonitis (4.04 log)	340	FOS	Suppressed (16 days)	1.8	Relapsed off FOS. Retreated with FOS + CMV Ig + RAP	9	Relapse
11	UL97 M460I (GCV) UL54 L545S (CID)	Pneumonitis and GI (5.53 log)	3	FOS, CMV Ig	Not suppressed	NA	Died of pneumonitis (28 days)	NA	Failure
12	UL97 M460V (GCV)	Pneumonitis (4.00 log)	366	FOS, CMV Ig, RAP	Not suppressed	NA	Pneumonitis responded to FOS + GCV + CMV Ig + RAP + CMX-001, but ongoing viremia.	7	Failure
13	UL97 L595S, C603W/C (GCV)	Pneumonitis and GI (3.62 log)	25	FOS, CMV Ig	Suppressed (16 days)	2.6	Multiple relapses, maintained on FOS	11	Relapse
14	UL97 M460I (GCV) UL54 F412L (CID)	Viremia (3.22 log)	260	FOS, CMV Ig, RAP	Suppressed (20 days)	2.1	Relapsing viremia on RAP maintenance	4	Relapse
15	UL97 C603W (GCV) UL54 K513N (CID)	Viremia (3.52 log)	145	FOS, GCV, CMV Ig, RAP	Suppressed (146 days)	49.9	Relapsed on VGC + CMV Ig + RAP. Persistent viremia on VGC + RAP	21	Relapse
16	UL97 C603W (GCV) UL54 L501F (CID)	Viremia (4.30 log)	NA	FOS, LEF	Suppressed (80 days)	10	Relapsed on LEF. Retreated with FOS	7	Relapse
Treated with IV ganciclovir									
6	UL97 C603W (GCV)	Viremia (4.23 log)	48	GCV, then VGC	Suppressed (20 days)	2.2	Multiple relapses off antivirals, treated with VGC	47	Relapse
4	UL97 (GCV)[b]	Pneumonitis and GI infection (4.23 log)	162	GCV, then VGC	Suppressed (20 days)	2.4	Sustained suppression off antivirals	43	Success

[a] Abbreviations: GCV, ganciclovir; FOS, foscarnet; LEF, leflunomide; CID, cidofovir; RAP, rapamycin; CMV Ig, CMV immune globulin; NA, not applicable.
[b] Codon information not provided.

Minces LR et al. Antimicrob Agents Chemother 2014;58(1):128-35.

Spesifik monoklonal antikorlar

Phase 2 Randomized, Double-Blind, Placebo-Controlled Trial of RG7667, a Combination Monoclonal Antibody, for Prevention of Cytomegalovirus Infection in High-Risk Kidney Transplant Recipients



- Randomize, çift kör, plasebo kontrolü çalışma
- RG7667, iki monoklonal antikor kombinasyonu
- Yüksek riskli böbrek transplantasyon hastaları
- Postransplantasyon 12-24 haftalarda plaseboya göre daha düşük CMV infeksiyonu

Ishida JH, et al.Antimicrob Agents Chemother 2017 Jan 24;61(2).

Diğer herpes virüs infeksiyonlarında tedavi

Varisella- zoster virüs infeksiyonları

- Asiklovir
- Valasiklovir
- Famsiklovir
- Brivudin

- Foscarnet
- Vidarabin
- İnterferon

Transpl Infect Dis. 2016 Oct;18(5):785-790. doi: 10.1111/tid.12583. Epub 2016 Sep 16.

Brincidofovir treatment of acyclovir-resistant disseminated varicella zoster virus infection in an immunocompromised host.

Mullane KM[1], Nuss C[2], Ridgeway J[2], Prichard MN[3], Hartline CB[3], Theusch J[2], Mommeja-Marin H[4], Larson RA[2].

Author information

Abstract

Brincidofovir (BCV) is a broad-spectrum antiviral agent active in vitro against double-stranded DNA viruses including herpesviruses, adenoviruses, polyomaviruses, and poxviruses. We report successful BCV use in management of disseminated acyclovir- and cidofovir-resistant varicella zoster virus in an immunocompromised hematopoietic stem cell transplant patient with chronic graft-versus-host disease who was intolerant to foscarnet.

HHV-6 infeksiyonlarında tedavi

- Gansiklovir (HHV-6B'ye etkili, 6A?)
- Foskarnet (HHV-6A ve 6B'ye etkili)
- Gansiklovir + foskarnet
- UL69 protein kinaz mutasyonu nedeniyle gansiklovir direnci gelişebilir

- T hücreli immunoterapi?

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Epstein-Barr virüs

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Lytic Induction Therapy for Epstein-Barr Virus-Positive B-Cell Lymphomas

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A novel therapy for Epstein-Barr virus (EBV)-positive tumors involves the intentional induction of the lytic form of EBV infection combined with ganciclovir (GCV) treatment. Virally encoded kinases (thymidine kinase and BGLF4) which are expressed only during the lytic form of infection convert GCV (a nucleoside analogue) into its active, cytotoxic form. However, tightly latent EBV infection in B cells has made it difficult to identify drugs that can be used clinically to induce lytic viral infection in B-cell lymphomas. Here we demonstrate that

- Latent infekte hücrelerde litik replikasyonu aktive etmek
- Daha sonra litik replikasyon inhibitörleri (asiklovir, gansiklovir gibi) kullanmak

HHV-8

- Gansiklovir
- Valgansiklovir
- Foskarnet
- Sidofovir

in vitro etkili

Herpes B virus

- Gansiklovir
- Asiklovir

İlginiz için teşekkürler