VI Congreso SEICAV

Sociedad Española de Infecciones Cardiovasculares

14:15-15:15. Simposio 2 SEICAV: Tratamiento antibiótico domiciliario endovenoso (TADE) y la endocarditis infecciosa.

Moderadores:

Miguel Ángel Goenaga. Hospital Universitario Donostia, San Sebastián, Guipúzcoa.

Nieves Sopena. Hospital Universitario Germans Trias i Pujol de Badalona. Barcelona.

- 14:15-14:35. **Qué pacientes con endocarditis infecciosa pueden ir a tratamiento antibiótico domiciliario endovenoso (TADE).**
  Mª Eugenia García Leoni. Hospital Universitario Gregorio Marañón. Madrid.
- 14:35-14:55. **Nuevas opciones terapéuticas: papel Dalbavancina.**
  M.C. Fariñas. Hospital Universitario Marqués de Valdecilla, Santander.
- 14:55-15:15. **Discusión Simposio 2**

Systemic Antibacterials: Recent FDA Approvals

- 2009
  -Telavancin (*Vibativ*): SSTI
- 2010
  - Ceftaroline (*Teflaro*): SSTI, CAP
- 2011
  - Fidaxomicin (*Dificid*): *Clostridium difficile*
- 2013
  - Telavancin (*Vibativ*): HAP/VAP
- 2014
  Tedizolid (*Sivextro*): SSTI
  Dalbavancin (*Dalvance*): SSTI
  Oritavancin (*Orbactiv*): SSTI

- ✓ **Nuevas Opciones terapéuticas de la EI en el Domicilio**

-Ceftarolina
-Tedizolid
-Dalbavancina

Ceftarolina fosamil.

- **FDA:** Octubre de **2010,** aprobó su utilización para su uso en adultos
- **EMA** en Europa en **2012**.

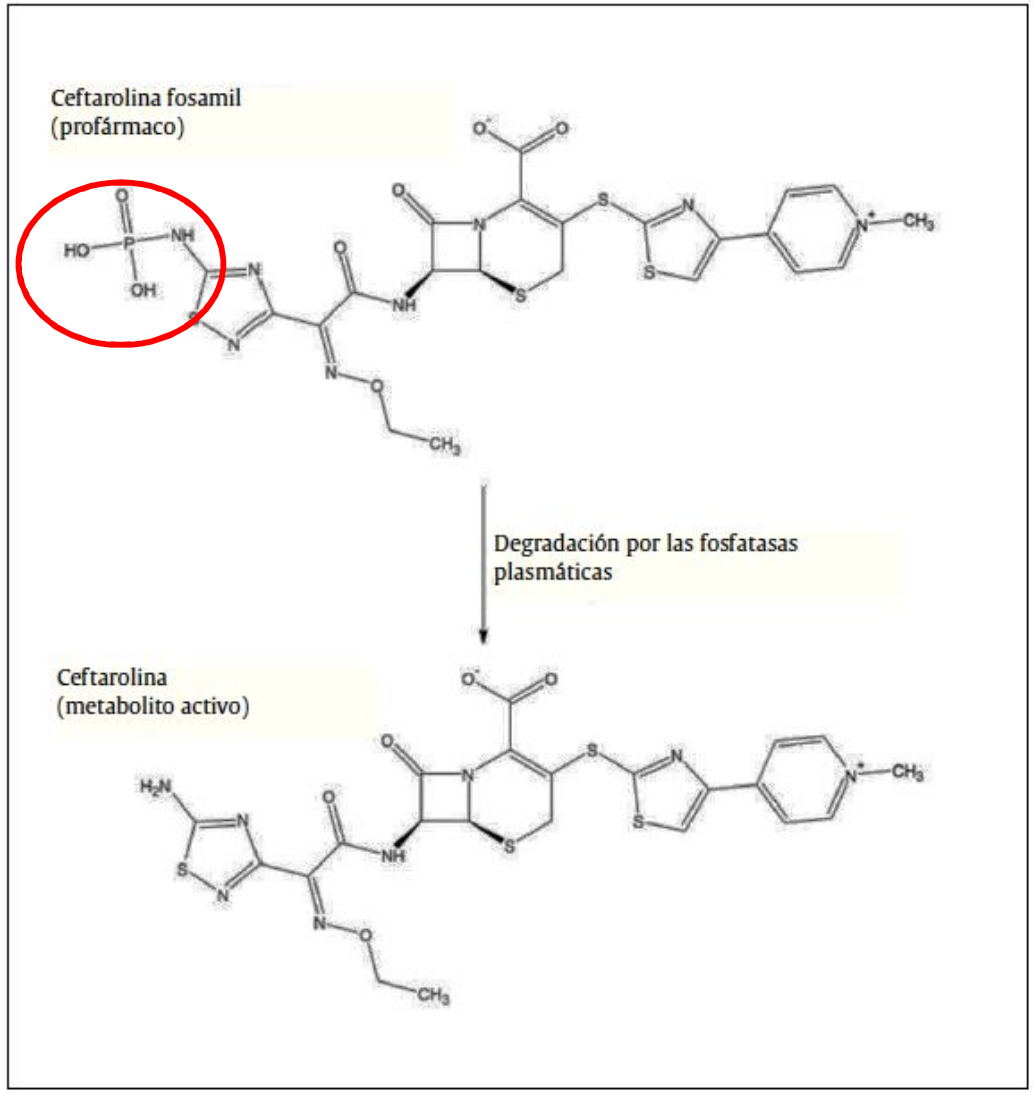
✓**Infecciones complicadas de la piel y tejidos blandos**

✓**Neumonía adquirida en la comunidad (NAC)**

¿QUÉ ES CEFTAROLINA ?

Cefalosporina de 5ª generación

1º antibiótico betalactámico util n infecciones por SARM



- Molécula con muy escasa solubilidad en agua, por lo que para poder utilizarla para su administración parenteral precisa de la adición de un **grupo fosfato** que permite su solubilidad.

- La **ceftarolina fosamil** se convierte rápidamente en su metabolito activo, **la ceftarolina**, por la acción de las enzimas fosfatasas sanguíneas.

hemother 2012; **67**: 1267–1270
c/dks006 Advance Access publication 6 February 2012

Journal of Antimicrobial Chemotherapy

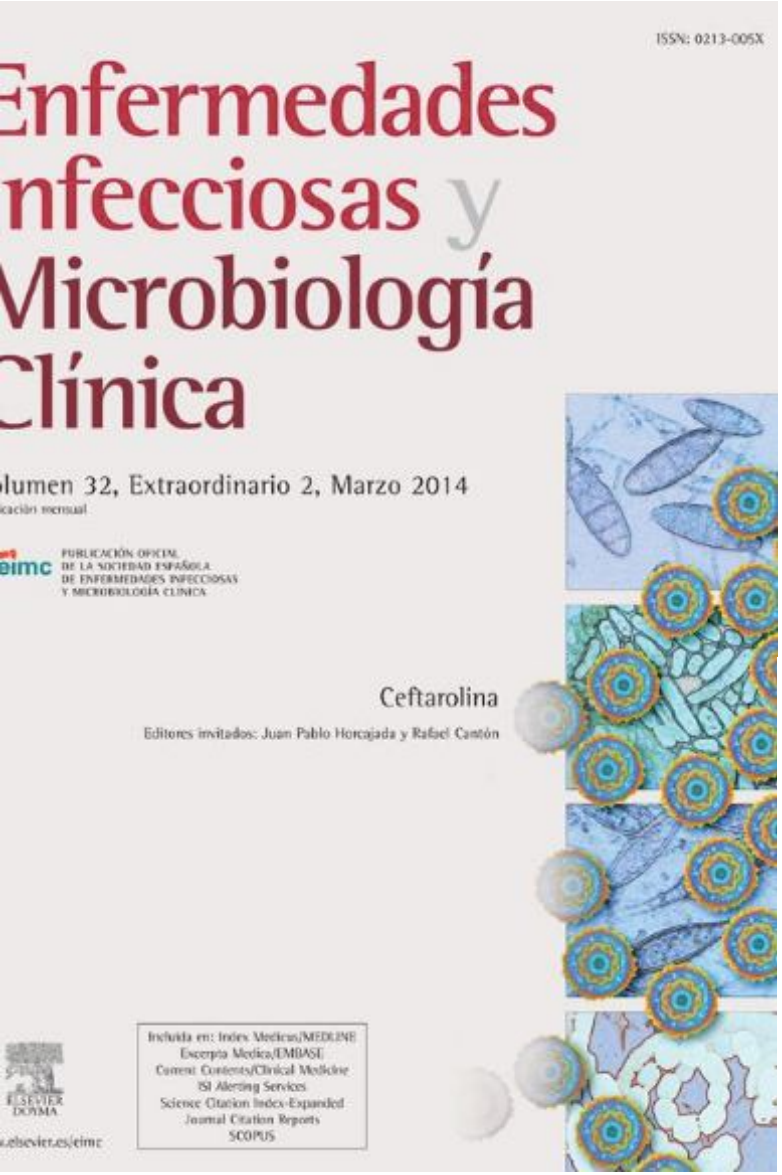
Methicillin-resistant *Staphylococcus aureus* bacteraemia and endocarditis treated with ceftaroline salvage therapy

T. Ho[1], Jose Cadena[1,2], Lindsey M. Childs[2,3], Miguel Gonzalez-Velez[1] and James S. Lewis II[1,3,4]*

Table 1. Summary of cases and outcomes

Case	Source of MRSA bacteraemia	Duration of bacteraemia (days)	Prior therapy (days)	VAN MIC (mg/L)[a]	DAP MIC (mg/L)[a]	Linezolid MIC (mg/L)[a]	Ceftaroline MIC (mg/L)[a], dose/duration[b]	Complications	Cl ou
1	endocarditis	13 days, cleared and relapsed day 17, cleared on day 18 (start of ceftaroline therapy)	13 (VAN), then 4 (DAP)	day 17: 4	2	NA	0.5—VISA isolate, 600 mg iv q8h for 42 days	mitral valve replacement, ESBL *Klebsiella pneumonia* bacteraemia; responded to 10 days of meropenem	resc
2	endocarditis	15	15 (VAN)	1.5	0.5	1	0.5, 600 mg iv q8h ×3 weeks, then linezolid 600 bid ×3 weeks	none	resc
3	skin and soft tissue, uveitis, endocarditis	2[c]	22 (VAN)	2	NA	NA	0.5, 600 mg q8h ×3 weeks, then linezolid 600 mg orally bid ×3 weeks	none	resc
4	urinary tract infection	11	11 (VAN)	2	2	0.5	0.5, 600 mg q12h for 10 days	GI bleeding	dea
5	uveitis, ethmoid osteomyelitis	13	12 (VAN)	2	1	2	0.5, 600 mg q8h for 2 weeks, then VAN for 4 weeks	none	resc
6	prostatitis, septic thrombophlebitis	13	8 (VAN)	1.5	1	2	0.5, 600 mg q8h for 22 days, then VAN to finish 6 weeks	none	resc

bid, twice daily; DAP, daptomycin; ESBL, extended-spectrum β-lactamase; GI, gastrointestinal; iv, intravenously; NA, not available; q8h, every 8 h; q12h, every 12 h; VAN, vanc
VISA, vancomycin-intermediate *S. aureus*.
[a]All MICs determined using Etest.
[b]All ceftaroline infusions administered over 1 h. No ceftaroline therapeutic drug monitoring was performed.
[c]Progression of ocular lesions while on therapy with vancomycin and appearance of new pulmonary nodules/lesions consistent with embolization.



Enferm Infecc Microbiol Clin. 2014;32(Supl 2):44-53

ELSEVIER DOYMA

Enfermedades Infecciosas y Microbiología Clínica

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Papel de la ceftarolina fosamil en el tratamiento de la bacteriemia y la endocarditis infecciosa

Benito Almirante[a,*], Juan M. Pericás[b] y José M. Miró[b]

[a]Servicio de Enfermedades Infecciosas, Hospital Universitari Vall d'Hebron, Barcelona, España
[b]Servicio de Enfermedades Infecciosas, Hospital Clínic, Universidad de Barcelona, Barcelona, España

RESUMEN

La ceftarolina fosamil es una nueva subclase de las cefalosporinas con una actividad intrínseca frente a diversos microorganismos grampositivos multirresistentes, entre ellos *Staphylococcus* *Streptococcus pneumoniae*, y frente a enterobacterias causantes de bacteriemia y endocarditis infe perfil farmacocinético y las características farmacodinámicas convierten a este fármaco en una b ción terapéutica para este tipo de infecciones. En los estudios experimentales se ha comprobado u eficacia para el tratamiento de las endocarditis producidas por *S. aureus*, con independencia de su dad a meticilina o vancomicina. La experiencia clínica es limitada, aunque en los ensayos clínicos series clínicas comunicadas se ha observado una respuesta clínica favorable en pacientes con bac relacionada con infecciones de piel y partes blandas, neumonía o endocarditis infecciosa. En estud ros se deberá definir con precisión el papel de este nuevo antibiótico para la terapia de estas infec

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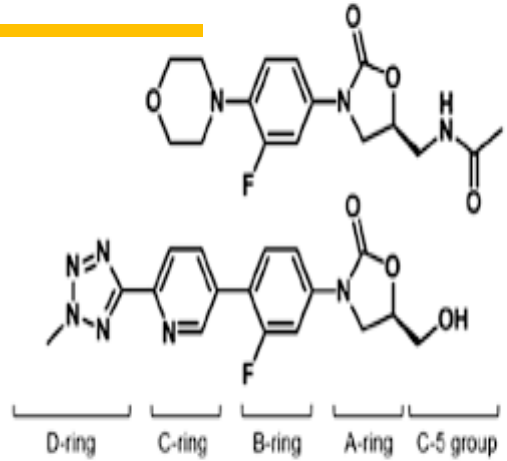
TEDIZOLID



- Antibiótico de 2º generación perteneciente al grupo de las **Oxazolidinonas**.
- Inhibe la síntesis de proteínas impidiendo la unión de N-formilmetionil- ARNt al ribosoma.
- Se usa para tratar **infecciones** agudas de **piel** en adultos ocasionadas por SARM, *S.aureus* sensible a meticilina, varias especies de *S.pyogenes* y *E. fecalis*.
- Antibiótico **BACTERIOSTÁTICO**.
- X4-X16 veces más potente que el Linezolid.
- Se administra 1 vez al día, a diferencia del Linezolid que son 2 veces al día.
- **Efectos adversos:** Náuseas, vómitos, diarrea, mareos y dolor de cabeza.

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June 2015 Volume 59 Number 6

Comparative Efficacies of Tedizolid Phosphate, Vancomycin, and Daptomycin in a Rabbit Model of Methicillin-Resistant *Staphylococcus aureus* Endocarditis

Liana C. Chan,[a,b] Li Basuino,[a] Etyene C. Dip,[a] Henry F. Chambers[a]

Division of Infectious Diseases, San Francisco General Hospital, San Francisco, California, USA[a]; Division of Molecular Medicine, Harbor-UCLA Medical Center, Torrance, California, USA[b]

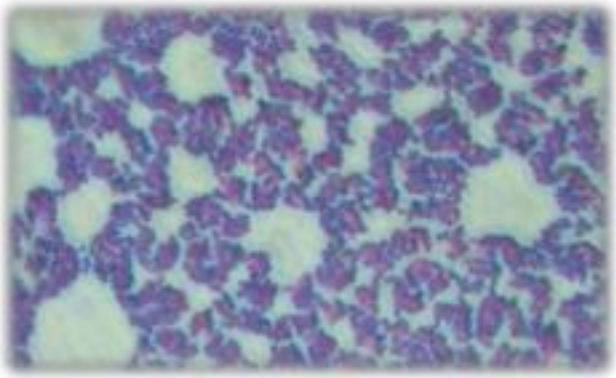
Tedizolid, the active component of the prodrug tedizolid phosphate, is a novel oxazolidinone that is approximately 4 times more active by weight than linezolid against *Staphylococcus aureus in vitro*. The *in vivo* efficacy of tedizolid phosphate (15 mg/kg body weight intravenous [i.v.] twice a day [b.i.d.]) was compared to those of vancomycin (30 mg/kg i.v. b.i.d.) and daptomycin (18 mg/kg i.v. once a day [q.d.]) in a rabbit model of aortic valve endocarditis (AVE) caused by methicillin-resistant *S. aureus* strain COL (infection inoculum of 10^7 CFU). Median vegetation titers of daptomycin-treated rabbits were significantly lower than those of rabbits treated with tedizolid phosphate (15 mg/kg b.i.d.) ($P = 0.016$), whereas titers for vancomycin-treated compared to tedizolid-treated rabbits were not different ($P = 0.984$). The numbers of organisms in spleen and kidney tissues were similar for all treatment groups. A dose-ranging experiment was performed with tedizolid phosphate (2, 4, and 8 mg/kg b.i.d.) compared to vancomycin (30 mg/kg b.i.d.), using a higher infecting inoculum (10^8 CFU) to determine the lowest efficacious dose of tedizolid phosphate. Tedizolid phosphate (2 mg/kg) (equivalent to 60% of the area under the concentration-time curve from 0 to 24 h (AUC_{0-24}) for the human 200-mg dose approved by the U.S. Food and Drug Administration) was not efficacious. Tedizolid phosphate at 4 mg/kg (equivalent to 75% of the AUC_{0-24} for the human 400-mg dose) and 8 mg/kg produced lower vegetation titers than the control, but neither was as efficacious as vancomycin.

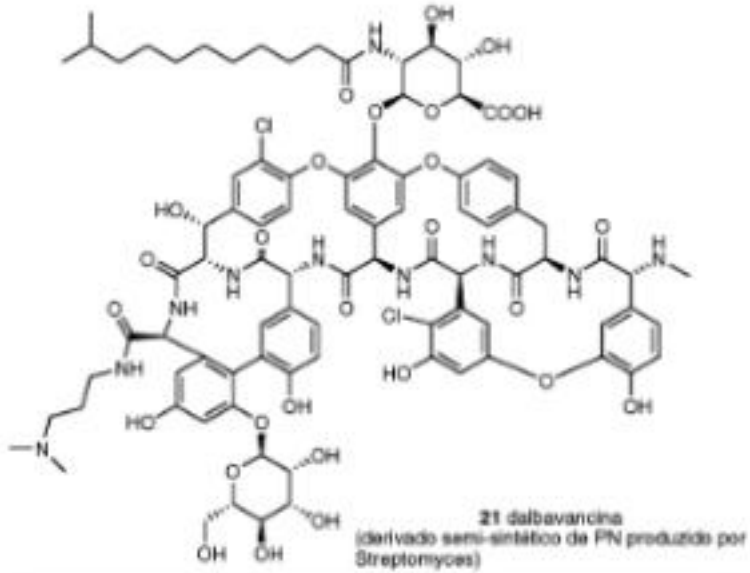
Dalbavancina

GENERALIDADES

Dalbavancina

La dalbavancina es un glicopéptido que se destaca por su gran eficacia *in vivo* frente a Gram positivos.





fppt.com

Glicopéptidos

DALBAVANCIN	TELAVANCIN	ORITAVANCIN
• Lipoglicopéptido • Derivado de la teicoplanina • Inhibe la síntesis de la pared celular • Activo frente a SARM • T ½ -- 6-10 días. • 1d/s→ dosis semanal • 1000 mg día 0 y 500 mg/dia 8 • In vitro inhibe > 98% de bacterias gram+ (> 6000) • Naúseas, diarrea, estereñimiento	• Lipoglicopéptido • Derivado de la Vancomicina • Mecanismo dual (inhibe la síntesis de la pared + despolariza la membrana) • Actividad bactericida rápida • Activo frente a SARM • T ½ --7-9 h • 7.5-10 mg7Kg/día • Nauseas, alteraciones del gusto, trastorno del sueño	• Glicopéptido semisintético • Espectro similar a Vancomicina • Activo SARM y SARV • T ½ 100h • 1 dosis cada 24-48 horas • Alteración del potencial transmembrana • Fase III: No diferencias Vancomicina vs Oritavancin

Dalbavancin (*Dalvance*)

- FDA Status: approved May 23, 2014
- Clinical Indication: approved for SSTI caused by gram-positive bacteria (MSSA, MRSA, *S. pyogenes*, *S. agalactiae*, *S. anginosus* group)
- Mechanism: Lipoglycopeptide that inhibits cell wall synthesis
- 2 Dose Regimen: 1000 mg IV followed 1 week later by 500 mg IV
- Dose Reduction:
  - Regular hemodialysis: no dose change
  - For CrCl < 30 ml/min and no hemodialysis: 750 mg then 375 mg
- Adverse Effects: nausea, headache, diarrhea

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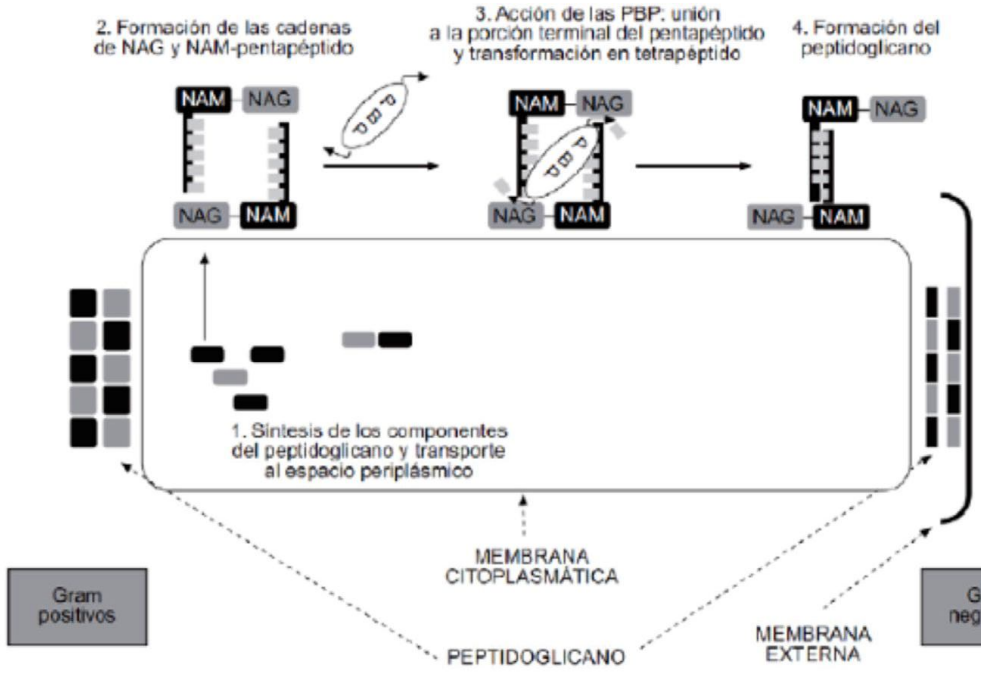
INFORME DE POSICIONAMIENTO TERAPÉUTICO
PT-DALBAVANCINA/V1/21012016

Informe de Posicionamiento Terapéutico de dalbavancina (Xydalba®)

Fecha de publicación: 21 de enero de 2016

Recordar…Mecanismo de acción glucopétido

- Inhiben la síntesis del peptidoglicano en un paso metabólico previo al de los β-lactámicos, uniéndose a los precursores e impidiendo su formación.



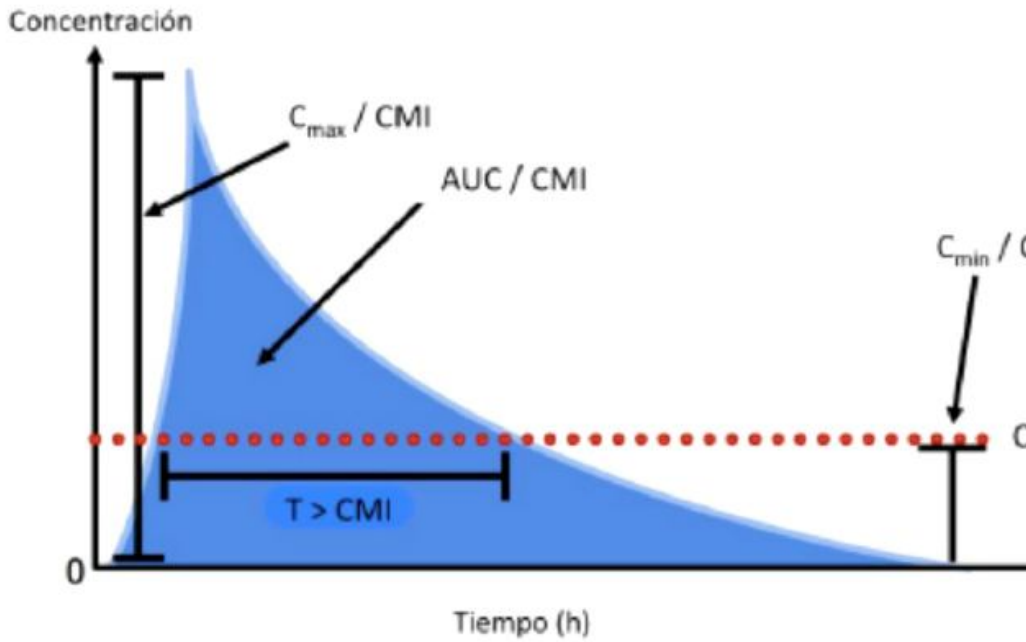
NAM: Ácido N-acetilmurámico; NAG: Ácido N-acetilglucosamina; PBP: Penicillin Binding Protein

Recordar…Mecanismo de acción glucopétido

Efecto **bactericida** lento tiempo-dependiente sobre población sensible en fase de replicación activa.

La eficacia clínica se correlaciona con el tiempo de permanencia por encima de la CMI (T>CMI) y especialmente con el valor del ABC24h/CMI.

- **Concentración-dependiente con dependencia del tiempo:** Su efecto se mediante la relación entre el ABC alcanzado en un periodo de 24 horas y la CM microorganismo (ABC_{24h}/CMI).



PRINCIPALES CARACTERÍSTICAS

nión a proteínas 93%

d 0,1-0,2 l/kg

etabolismo — 15% hidroxilación
No es sustrato P450

liminación — 20% heces
19-33% renal no modificada y 8-12% renal en forma de hidroxi-dalbavancina.

oblaciones especiales

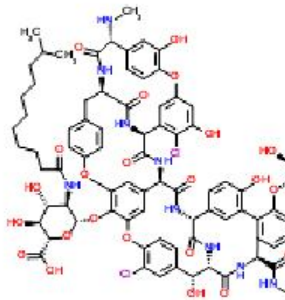
- Insuf. Renal
- Insuf. Hepática
- Sexo
- Ancianos
- Población pediátrica

Estimated CrCl	DALVANCE 1 DOSE	DALVANCE 2 DOSE
≥30 mL/min or on regular hemodialysis	1500 mg	1000 mg followed 1 week later by 500 mg
<30 mL/min and not on regular hemodialysis	1125 mg	750 mg followed 1 week later by 375 mg

eacciones cruzadas con otros glucopéptidos (que no resistencias): casos de Colitis pseudomembranosa; Tambi

acciones similares al síndrome del hombre rojo.

Dalbavancina. Resumen



- Lipoglupéptido semisintético que inhibe la síntesis de la pared celular, de manera similar a como actúan los glucopéptidos.
- Es activo frente a la gran mayoría de bacterias Gram positivas, neumococos y enterococos.
- No activa para las cepas de enterococos R a Vancomicina por expresión del gen VanA.
- Es **bactericida** tiempo-dependiente.
- La vía de eliminación es mixta, eliminándose en **30-40% por orina**, requiriendo ajuste de dosis en casos de insuficiencia renal grave.
- Tiene una **semivida de eliminación prolongada (6-12 días)** por lo que se puede administrar una vez a la semana.

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INFORME DE POSICIONAMIENTO TERAPÉUTICO
PT-DALBAVANCINA/V1/21012016

Informe de Posicionamiento Terapéutico de dalbavancina

CONCLUSIÓN

Dalbavancina, a la dosis de 1000 mg en el día 1 y 500 mg en día 8, ha demostrado su eficacia, en base a criterios de no inferioridad, frente a vancomicina (1000 mg/ 12 h/ 14 días) con posibilidad de cambio a terapia oral con linezolid (600 mg/12 h) a partir del tercer día.

Respecto al perfil de seguridad, es aceptable y similar al que

CONSIDERACIONES FINALES DEL GCPT

Dado que no se han encontrado diferencias clínicamente relevantes entre la eficacia y seguridad del medicamento evaluado y sus alternativas, la elección entre ellos se basará fundamentalmente en criterios de eficiencia.

hospitalización, se contemple el manejo extrahospitalario de la infección, dalbavancina constituye una alternativa terapéutica al tratamiento secuencial con linezolid oral.

Dalbavancina

PIEL Y PARTES BLANDAS

[redacted]

2003:37 (15 November)

e-Weekly Dalbavancin versus Standard-of-Care microbial Regimens for Treatment of Skin Soft-Tissue Infections

tzer, Mary Beth Dorr, Beth P. Goldstein, Marc Perry, James A. Dowell, Tim Henkel, and the Dalbavancin Soft-Tissue Infection Study Group[a]

rmaceuticals, King of Prussia, Pennsylvania

ncin, a novel glycopeptide with a long elimination half-life (~9–12 days), was compared to standard obial therapy for skin and soft-tissue infections (SSTIs). In a randomized, controlled, open-label, phase of-concept trial, adults received 1100 mg of dalbavancin (as a single intravenous infusion), 1000 mg vancin intravenously and then 500 mg intravenously 1 week later, or a prospectively defined standard-egimen. A gram-positive pathogen was isolated from samples obtained from 41 (66%) of 62 patients ne; *Staphylococcus aureus* was the most prevalent species (83% of pathogens). Clinical success rates w-up visit (test of cure) were 94.1% among patients treated with 2 doses of dalbavancin, 61.5% among treated with 1 dose of dalbavancin, and 76.2% among patients treated with a standard-of-care regimen. ment regimens were well tolerated; drug-related adverse reaction rates were similar across the 3 groups. dings suggest that a regimen of 2 doses of dalbavancin administered 1 week apart is effective in the t of complicated, gram-positive bacterial SSTIs and warrants further study.

tandard-of-Care Antibiotics: Ceftriaxone, efazolin, Piperacillin and tazobactam, indamycin, Vancomycin, Linezolid, Cephalexin

CURACIÓN CLÍNICA:
94.1% pacientes tratados con 2 dosis de DAL
61.5% pacientes tratados con 1 dosis de DAL
76.2% pacientes tratados con regimen estandard

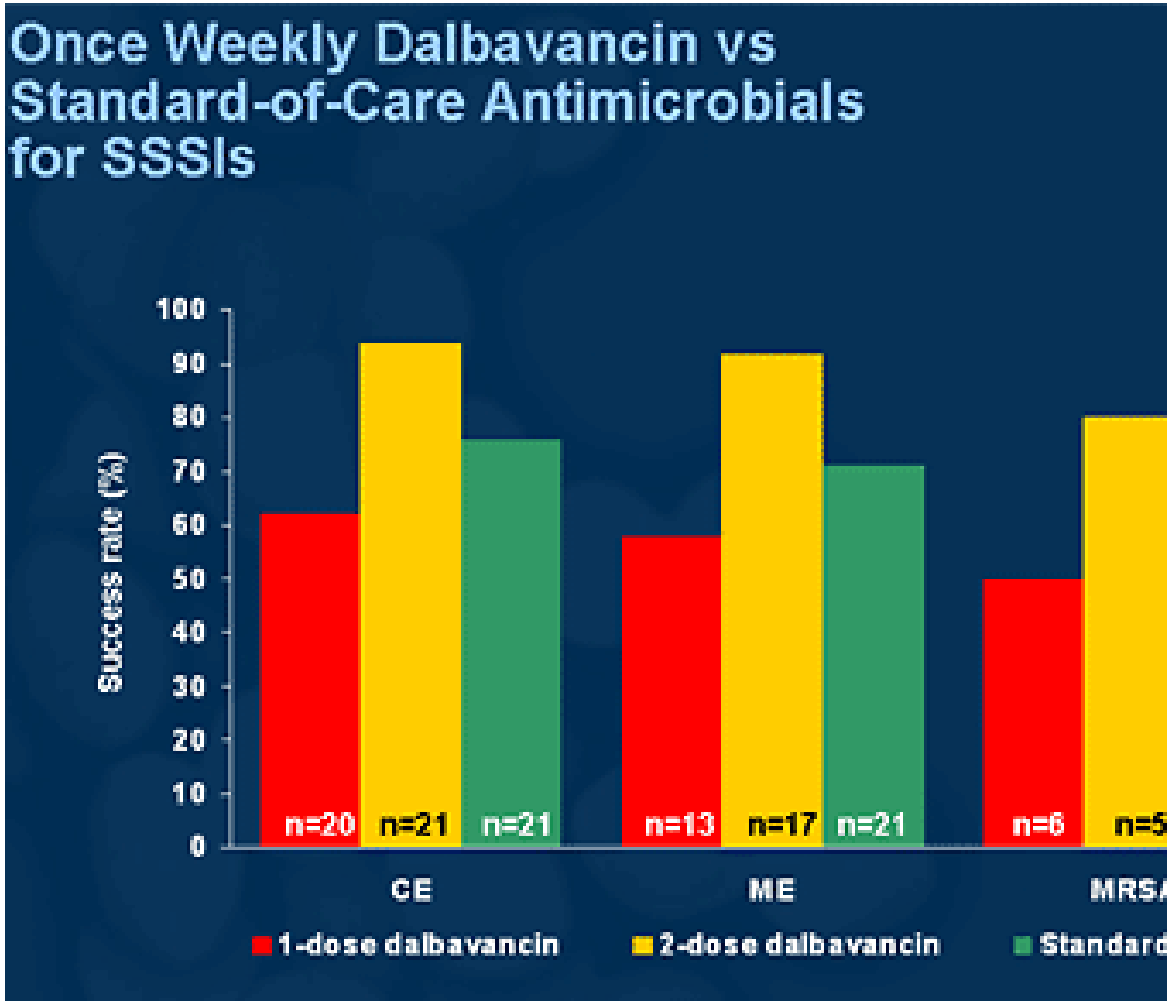


Table 3. Gram-positive pathogens isolated from samples obtained at baseline from patients with skin and soft-tissue infections (microbiological intent-to-treat population).

Pathogen	No. of patients with pathogen[a] in indicated treatment group		
	1-Dose dalbavancin (n = 14)	2-Dose dalbavancin (n = 13)	Comparator (n = 14)
Staphylococcus aureus	13	11	10
Methicillin-resistant *S. aureus*	6	5	2
Group B streptococcus	0	2	2
Streptococcus pyogenes	0	1	1
Miscellaneous *Streptococcus* and other species[b]	3	2	4

[a] More than 1 pathogen was detected in some patients at baseline.
[b] Includes β-hemolytic (nontypeable), group C, group G, and viridans streptococci and *Peptostreptococcus*.

CID 2005:41 (15 November)

andomized, Double-Blind Comparison f Once-Weekly Dalbavancin versus Twice-Daily nezolid Therapy for the Treatment of Complicated kin and Skin Structure Infections

E. Jauregui,[1] Simon Babazadeh,[2] Elyse Seltzer,[5] Lisa Goldberg,[5] Dainis Krievins,[7] Mark Frederick,[3] d Krause,[5] Igors Satilovs,[8] Zilvinas Endzinas,[9] Jeffrey Breaux,[6] and William O'Riordan[4]

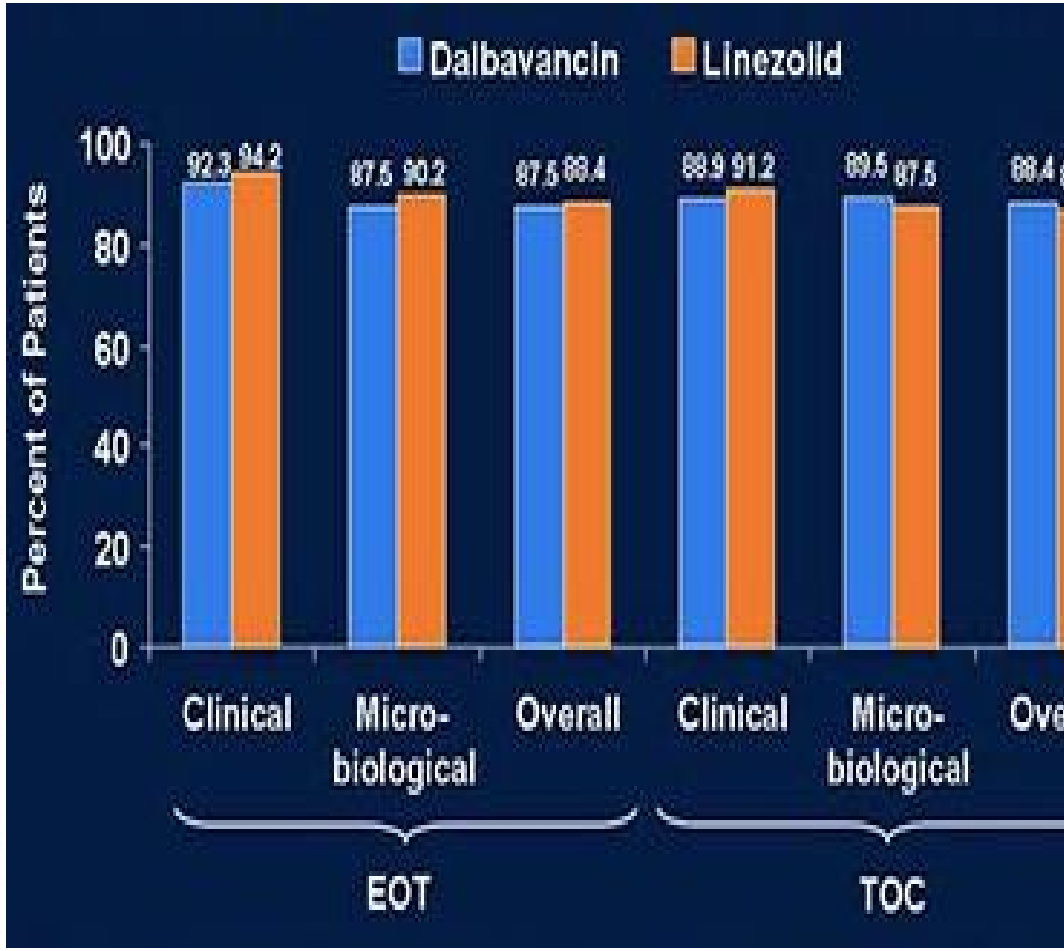
incent Mercy Medical Center, Toledo, Ohio; [2]Crest Clinical Trials, Anaheim, [3]Talbert Medical Group, Huntington Beach, and [4]eStudy Site, Vista, California; [5]Vicuron Pharmaceuticals, King of Prussia, Pennsylvania; [6]Gulf Coast Research Associates, Baton Rouge, Louisiana; adina University Hospital, Riga, and [8]Daugavpils Regional Hospital, Daugavpils, Latvia; and [9]Kaunas Medical University Hospital, s, Lithuania

ackground. Dalbavancin, a novel lipoglycopeptide with a pharmacokinetic profile that allows weekly dosing, tive against gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA). The efficacy albavancin for treatment of skin and skin structure infections (SSSIs) was demonstrated in a phase 2 study.

lethods. In a phase 3 noninferiority study, patients with complicated SSSIs, including infections known or ected to involve MRSA, were randomized (ratio, 2:1) in a double-blind manner to receive dalbavancin (1000 given intravenously on day 1 and 500 mg given intravenously on day 8) or linezolid (600 mg given intravenously ntravenously/orally every 12 h for 14 days). Efficacy was assessed by determining clinical and microbiological onses at the end of therapy and at the test-of-cure visit. Relapses were identified by additional follow-up ~1 th later.

esults. MRSA was identified in 51% of patients from whom a pathogen was isolated at baseline. Dalbavancin linezolid demonstrated comparable clinical efficacy in the clinically evaluable population at the test-of-cure (88.9% and 91.2% success, respectively). The rate of clinical success at the end of therapy was >90% in both s. Less than 1.0% of patients in either treatment arm experienced relapse after the test-of-cure visit. Both ments yielded successful microbiological response in excess of 85% among microbiologically evaluable patients nd of therapy and at the test-of-cure visit for all pathogens combined, for all *S. aureus* strains, and for MRSA. rointestinal symptoms were among the most common adverse events in both arms. A higher proportion of ents in the linezolid arm reported adverse events that were judged by the investigator to be probably/possibly ed to treatment (dalbavancin arm, 25.4% of subjects; linezolid arm, 32.2% of subjects).

onclusions. Two doses of dalbavancin (1000 mg given on day 1 followed by 500 mg given on day 8) were ell tolerated and as effective as linezolid given twice daily for 14 days for the treatment of patients with plicated SSSI, including those infected with MRSA.



Clinical, microbiological, and overall (combined clinical/microbiological) success at end-of-therapy (EOT) and test-of cure (TOC) visits.

The NEW ENGLAND JOURNAL of MEDICINE

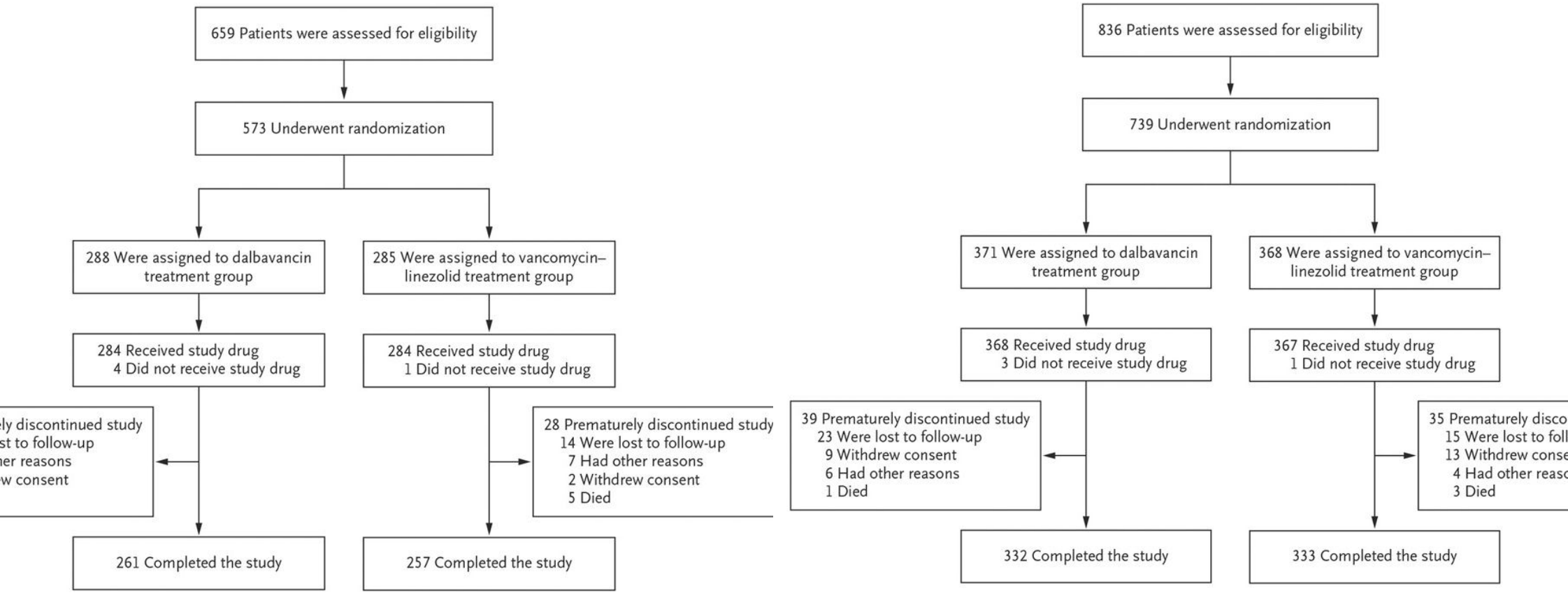
ESTABLISHED IN 1812 JUNE 5, 2014 VOL. 370 NO. 23

2011-2012

Once-Weekly Dalbavancin versus Daily Conventional Therapy for Skin Infection

Helen W. Boucher, M.D., Mark Wilcox, M.D., George H. Talbot, M.D., Sailaja Puttagunta, M.D., Anita F. Das, Ph.D., and Michael W. Dunne, M.D.

1



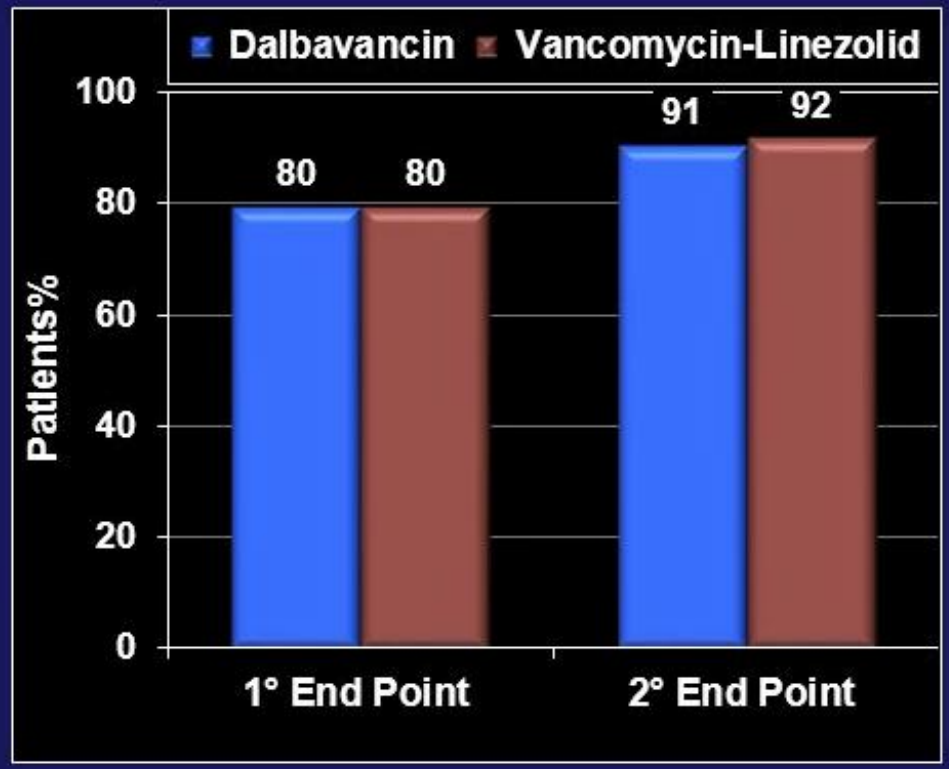
Dalbavancin versus Vancomycin for SSTI
DISCOVER 1 and DISCOVER 2

Study Design

- Methods
  - Pooled analysis of 2 phase 3 trials*
  - Randomized trials
  - N = 659 adults
  - Acute bacterial SSTI
- Regimens
  - Dalbavancin 1000 mg d1, 500 mg d8
  - Vancomycin IV for ≥3 days, then oral linezolid 600 mg bid to complete 10-14d

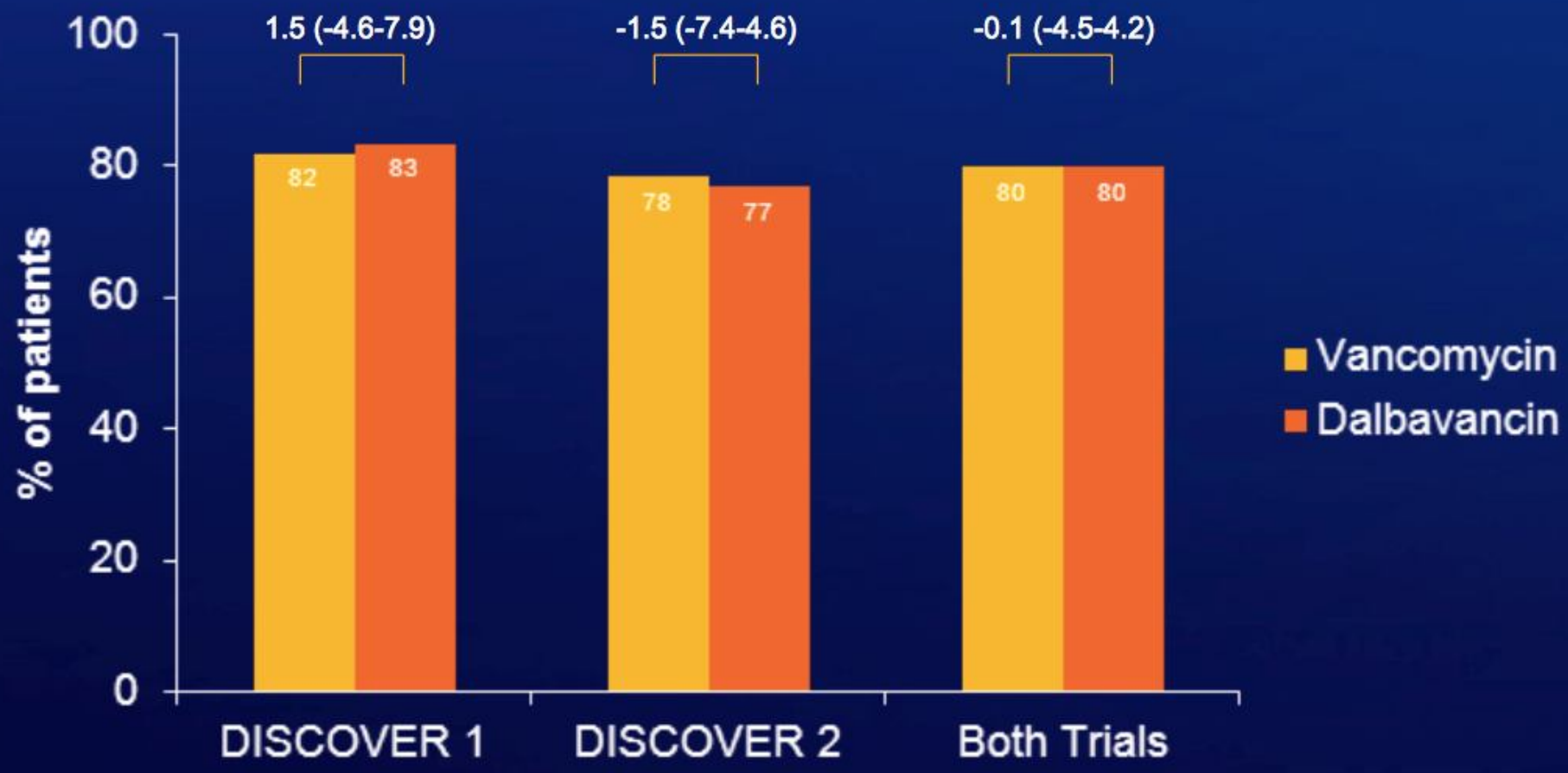
*DISCOVER 1 and DISCOVER 2

Clinical Response to Therapy



1° End Point = Success rate at 48 to 72 hours
2° End Point = Success rate at end of therapy

Treatment Success
DISCOVER 1 & 2



*Absolute difference (95% confidence interval)

Boucher HW et al. *N Eng J Med* 2014;370(23):2169-79.

Clinical Infectious Diseases 2016;62(5):545–51

A Randomized Clinical Trial of Single-Dose Versus Weekly Dalbavancin for Treatment of Acute Bacterial Skin and Skin Structure Infection

Michael W. Dunne,[1] Sailaja Puttagunta,[1] Philip Giordano,[2] Dainis Krievins,[3] Michael Zelasky,[1] and James Baldassarre[4]

[1]Allergan plc, Branford, Connecticut; [2]Orlando Health, Florida; [3]Stradins University Hospital, Riga, Latvia; and [4]Janssen Pharmaceuticals, Springhouse, Pennsylvania

Background. Acute bacterial skin and skin structure infections (ABSSSIs) are a cause of significant morbidity and therapy can be a burden to the healthcare system. New antibiotics that simplify treatment and avoid hospitalization are needed. This study compared the safety and efficacy of a single intravenous infusion of 1500 mg of dalbavancin to the 2-dose regimen.

Methods. This study was a randomized, double-blind trial in patients aged >18 years with ABSSSIs. Patients were randomized to dalbavancin 1500 mg either as a single intravenous (IV) infusion or 1000 mg IV on day 1 followed 1 week later by 500 mg IV. The primary endpoint was a ≥20% reduction in the area of erythema at 48–72 hours in the intent-to-treat population. Noninferiority was to be declared if the lower limit of the 95% confidence interval (CI) on the difference in the outcomes was greater than −10%. Clinical outcome was also assessed at days 14 and 28.

Results. Six hundred ninety-eight patients were randomized. Demographic characteristics were similar on each regimen, although there were more patients with methicillin-resistant *Staphylococcus aureus* (MRSA) at baseline on the 2-dose regimen (36/210 [17.1%] vs 61/220 [27.7%]). Dalbavancin delivered as a single dose was noninferior to a 2-dose regimen (81.4% vs 84.2%; difference, −2.9% [95% CI, −8.5% to 2.8%]). Clinical outcomes were also similar at day 14 (84.0% vs 84.8%), day 28 (84.5% vs 85.1%), and day 14 in clinically evaluable patients with MRSA in a baseline culture (92.9% vs 95.3%) in the single- and 2-dose regimens, respectively. Treatment-emergent adverse events occurred in 20.1% of the single-dose patients and 19.9% on the 2-dose regimen.

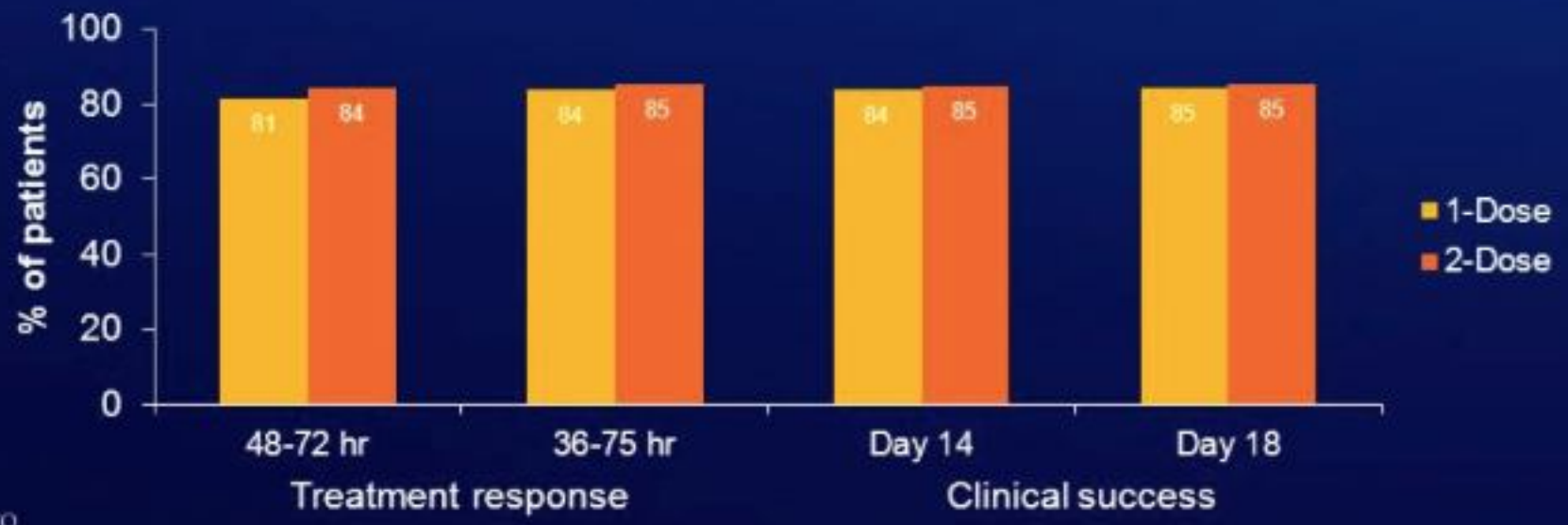
Conclusions. A single 1500-mg infusion of dalbavancin is noninferior to a 2-dose regimen, has a similar safety profile, and removes logistical constraints related to delivery of the second dose.

Dunne MW et al. (2016)

- Dose-exploration study in ABSSSI
  - 1500mg IV once
  - 1000mg IV on day 1 then 500mg IV on day 8

Dunne MW et al. (2016)

- Dose-exploration study in ABSSSI
  - 1500mg IV once
  - 1000mg IV on day 1 then 500mg IV on day 8
- No differences in adverse events up to 28 days



MAYO CLINIC

ABSSSI = Acute bacterial skin and skin structure infection

Dunne MW et al. *Clin Infect Dis* 2016;62(5):545-51.

Enferm Infecc Microbiol Clin. 2017;35(Supl 1):1

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Introducción

M. Ángeles Domínguez[a] y Alex Soriano[b]

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[b]Servicio de Infecciones, Hospital Clínic, Barcelona, España

de la daptomicina. La reciente comercialización de dalbavancin
nuevo lipoglucopéptido, supone un avance, principalmente p
gran actividad frente a estafilococos sensibles y resistentes a la m
lina, pero también gracias a una semivida de eliminación muy pr
gada, que permite una administración semanal por vía intrav
utilizando un catéter periférico y con un tiempo de infusión no
rior a los 30 min[9]. Esta nueva posología supone un cambio de pa
ma que requiere un conocimiento detallado del producto. El ob

Enferm Infecc Microbiol Clin. 2017;35(Supl 1):9-14

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tro antimicrobiano de dalbavancina. Mecanismo de acción y actividad
ro frente a microorganismos Gram positivos

Cercenado

Microbiología y Enfermedades Infecciosas, Hospital General Universitario Gregorio Marañón, Madrid, España
to de Medicina, Facultad de Medicina, Universidad Complutense, Madrid, España

Excelente actividad frente SARM y estreptococos del grupo viridans y S. pneumoniae resistentes a la penicilina.

NO tiene actividad frente a aquellas cepas de Enterococo que expresan el fenotipo de resistencia **VanA.**

Actualmente, más del 98% de las cepas frente a las que se ha estudiado la actividad de dalbavancina se inhiben por concentraciones 0,12 mg/l, que es el punto de corte de sensibilidad definido por elEUCAST.

Actividad lentamente **bactericida frente a *S. aureus*, ECN y *S. pyogenes*.**

Actividad in vitro de la dalbavancina frente a microorganismos Gram positivos obtenida en estudios de vigilancia a nivel mundial

Microorganismos (n)	CMI_{50} (mg/l)	CMI_{90} (mg/l)	Rango	Cepas sensibles (%)	Ra
Staphylococcus aureus (64.843)	0,06	0,06	≤ 0,008-0,5	99,7	10
SASM (37.222)	0,06	0,06-0,5	≤ 0,008-0,5	99,7	10
SARM (27.261)	0,06	0,06	≤ 0,008-1	99,6	10
SARM (5.167)	0,06	0,06	≤ 0,03-0,25	99,7	22
SANSD (37)	0,06	0,12	≤ 0,03-0,5	91,9	22
SARL (19)	0,06	0,12	≤ 0,03-0,12	100	22
SANST (38)	0,06	0,06	≤ 0,03-0,12	100	22
VISA (8)	0,5	ND	0,50-2	0	25
hVISA (10)	0,25	0,5	0,12-0,5	20	25
ECN (2.248)	≤ 0,03	0,06-0,12	≤ 0,03-1	> 99	10
ECN MS (963)	≤ 0,03	0,06-0,5	≤ 0,03-1	> 99	10
ECN MR (2.293)	≤ 0,03	0,06-0,5	≤ 0,03-1	> 99	10
ECN teicoplanina-R (15)	≤ 0,03	0,25	≤ 0,03-0,25	> 99	11
Enterococcus spp. (116)	0,06	> 4	≤ 0,03-> 4	56	20
ESV (663)	≤ 0,03	0,06-0,12	≤ 0,03-4	> 99	4,
ERV VanA (150)	> 4	> 4	0,25-> 4	0	20
ERV VanB (664)	≤ 0,03	0,12-1	≤ 0,03-2	> 99	20
ERV VanC (75)	≤ 0,12	≤ 0,12	≤ 0,12-0,5	> 99	32
E. faecalis VS (586)	≤ 0,03	0,06	≤ 0,03-4	> 99	10
E. faecalis VR (98)	> 4	> 4	≤ 0,03-> 4	< 1	10
E. faecium VS (88)	0,06	0,12	≤ 0,03-4	> 99	10
E. faecium VR (192)	> 4	> 4	≤ 0,03-> 4	< 1	10
Streptococcus pneumoniae (307) (PS = 106; PI = 96; PR = 105)	0,03	0,06	≤ 0,03-0,12	100	14
Streptococcus betahemolíticos (1.242)	≤ 0,03	≤ 0,03	≤ 0,03-0,25	98,6	6,
Streptococcus pyogenes (506)	≤ 0,03	≤ 0,03	≤ 0,03-0,12	100	6,
Streptococcus agalactiae (287)	≤ 0,03	0,12	≤ 0,03-0,25	94,4	6,
Streptococcus dysagalactiae (58)	≤ 0,03	≤ 0,03	≤ 0,03-0,12	100	21
Streptococcus grupo *viridans* (786)	≤ 0,03	≤ 0,03	≤ 0,03-0,25	99,7	6,
Streptococcus grupo *viridans* PI + PR (30)	≤ 0,03	≤ 0,03	≤ 0,03	100	10
Streptococcus anginosus (184)	≤ 0,03	0,06	≤ 0,03-0,06	100	21
Streptococcus bovis (16)	≤ 0,03	0,06	≤ 0,03-0,06	100	10
Bacillus anthracis (30)	0,06	0,25	≤ 0,03-0,5	ND	18
Corynebacterium spp. (63)	0,06-0,5	0,12-0,5	≤ 0,03-1	ND	10
Actinomyces spp. (38)	0,25	0,5	≤ 0,03-0,5	ND	15
Listeria monocytogenes (138)	≤ 0,03-0,06	≤ 0,03-0,06	≤ 0,03-0,12	ND	10
Clostridium spp. (45)	0,03-0,25	0,06-2	≤ 0,03-8	ND	15
C. perfringens (10)	0,06	0,12	0,03-0,12	ND	15
C. difficile (26)	0,25	0,25	0,12-0,5	ND	15
C. clostridioforme (14)	4	8	2,00-8	ND	15
Lactobacillus spp. (23)	0,5	> 32	0,06-> 32	ND	15
Eubacterium spp. (25)	0,25	1	0,06-2	ND	15
Propionibacterium spp. (15)	0,25	0,5	0,03-0,5	ND	15
Peptostreptococcus spp. (30)	0,12	0,25	≤ 0,03-0,5	ND	15
Otros cocos Gram positivos anaerobios (100)	0,03-0,06	0,12	≤ 0,03-0,25	ND	19

ECN: estafilococos coagulasa negativos; ERV: enterococos resistentes a la vancomicina; ESV: enterococos sensibles a la vancomicina; hVISA: *Staphylococcus a*

Ensayos clinicos que evalúan la eficacia de dalbavancina en el tratamiento de las infecciones de piel y tejidos blandos

	Seltzer et al[9]			Jauregui et al[10]		Boucher et al[11]		Dunne et al[12]	
						Estudios DISCOVER 1 y 2			
Tipo de estudio	Fase II			Fase III		Fase III		Fase III	
Período	2001-2002			2003-2004		2011-2012		2014-2015	
Grupos de tratamiento	Dalbavancina 1 dosis[a]	Dalbavancina 2 dosis[b]	Régimen estándar[c]	Dalbavancina 2 dosis[b]	Linezolid	Dalbavancina 2 dosis[b]	Vancomicina/ linezolid	Dalbavancina 1 dosis[a]	Dalbavancina 2 dosis[b]
Pacientes incluidos	N = 20	N = 21	N = 21	N = 571	N = 283	N = 659	N = 653	N = 349	N = 349
Pacientes en los que se identificó microorganismo, n	14 (70)	13 (61,9)	14 (66,6)	391 (68,5)	215 (75,9)	337 (51,1)	329 (50,4)	210 (60,2)	220 (63)
SARM, n (%)	6/14 (42,8)	5/13 (38,5)	2/14 (14,3)	181 (46,3)	97 (45,1)	90/337 (26,7)	67/329 (20,4)	36/210 (17,1)	61/220 (27,7)
SASM, n (%)	7/14 (50)	6/13 (46,2)	8/14 (57,1)	137 (35,0)	77 (35,8)	167/337 (49,5)	189/329 (57,4)	103/210 (49,0)	96/220 (43,6)
Streptococcus pyogenes, n (%)	0/14 (0)	1/13 (7,7)	1/14 (7,1)	19 (4,9)	12 (5,6)	37/337 (10,9)	36/329 (10,9)	6/210 (2,8)	12/220 (5,4)
Respuesta al tratamiento									
Éxito a las 48-72 h n/N (%)	–	–	–	–	–	525/659 (79,7)	521/653 (79,8)	293/349 (84%)	298/349 (85,4%)
Visita al final de tratamiento									
ITT n/N (%)	15/20 (75)	19//21 (91)	17/21 (81)	92,3%[d]	94,2%[d]	–	–	293/349 (84)	296/349 (84,8)
CE n/N (%)	13/16 (81)	16/17 (94)	17/21 (81)	–	–	–	–	267/302 (88,4)	270/302 (89,4)
Visita de seguimiento									
ITT n/N (%)	12/20 (60)	19/21 (91)	16/21 (76)	298/316 (94)	151/163 (93)	–	–	295/349 (84,5)	297/349 (85)
CE n/N (%)	8/13 (62)	16/17 (94)	16/21 (76)	–	–	–	–	250/271 (92,3)	247/267 (92,5)
Efectos adversos n (%)	11 (55%)	10 (48%)	12 (57%)	25,4 %[d]	32,2%[d]	80 (12,3)	89 (13,7)	70 (20,1)	69 (19,9)

CE: clínicamente evaluables; ITT: intencion de tratamiento; SARM: *Staphylococcus aureus* resistente a meticilina; SASM: *Staphylococcus aureus* sensible a meticilina.
[a]1.100 mg de dalbavancina administrada en dosis única por vía intravenosa.
[b]1.000 mg de dalbavancina por vía intravenosa seguidos de 500 mg 1 semana más tarde.
[c]Uno de los siguientes fármacos: ceftriaxona, cefazolina, piperacilina/tazobactam, clindamicina, vancomicina, linezolid o cefalexina individualmente o en combinación durante 7-21 días.

Dalbavancina

Osteomielitis

AAC
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April 2015 Volume 59 Number 4

xtended-Duration Dosing and Distribution of Dalbavancin into Bone nd Articular Tissue

chael W. Dunne,[a] Sailaja Puttagunta,[a] Craig R. Sprenger,[c]* Chris Rubino,[b] Scott Van Wart,[b] James Baldassarre[a]

rata Therapeutics, Inc., Branford, Connecticut, USA[a]; Institute for Clinical Pharmacodynamics, Latham, New York, USA[b]; PRACS Institute, Ltd., Fargo, North Dakota, USA[c]

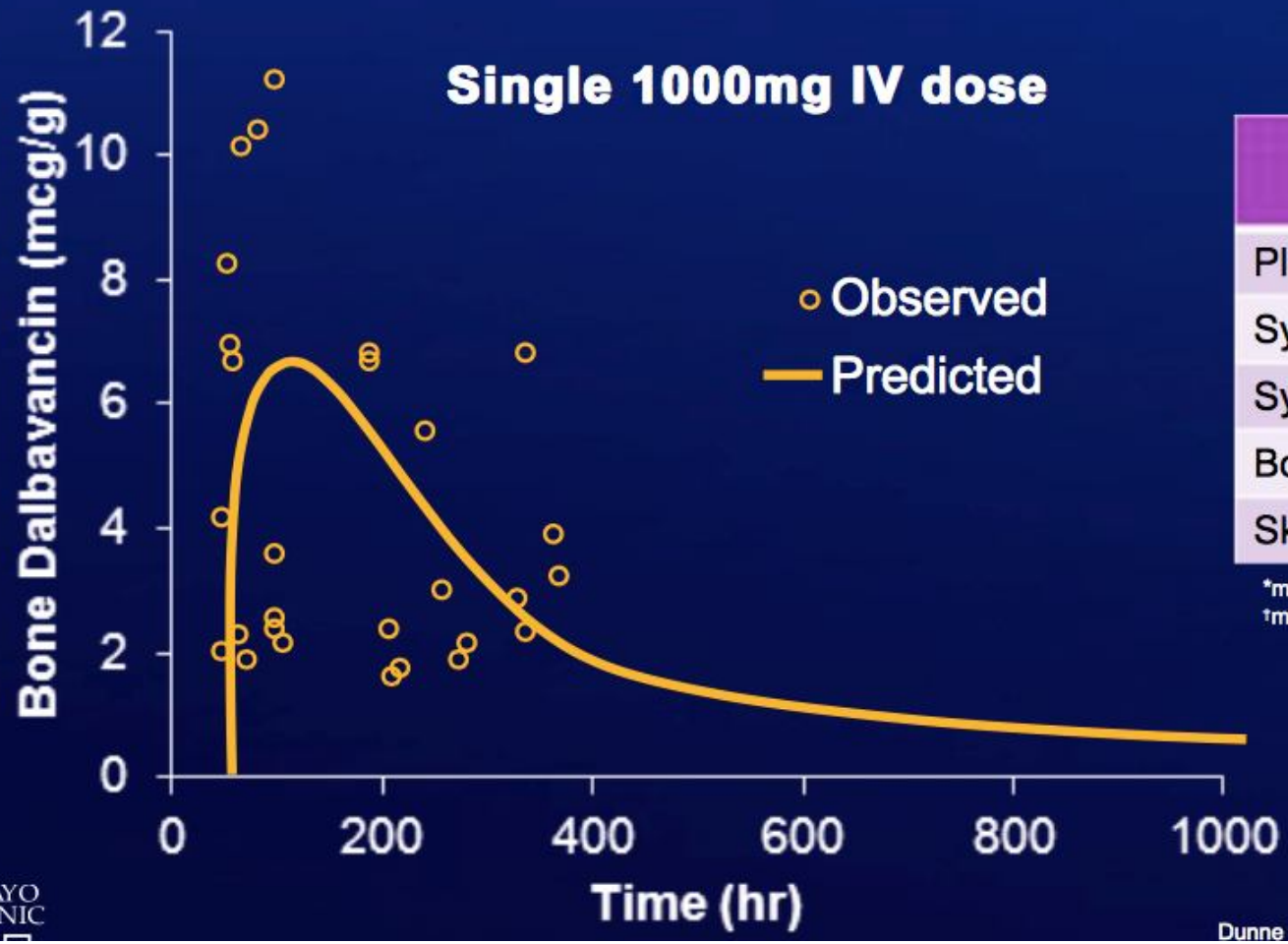
lbavancin is an intravenous lipoglycopeptide with activity against Gram-positive pathogens and an MIC_{90} for *Staphylococcus reus* of 0.06 μg/ml. With a terminal half-life of >14 days, dosing regimens with infrequent parenteral administration become ailable to treat infectious diseases such as osteomyelitis and endocarditis that otherwise require daily dosing for many weeks. order to support a rationale for these novel regimens, the pharmacokinetics over an extended dosing interval and the distri- tion of dalbavancin into bone and articular tissue were studied in two phase I trials and pharmacokinetic modeling was per- rmed. Intravenous administration of 1,000 mg of dalbavancin on day 1 followed by 500 mg weekly for seven additional weeks s well tolerated and did not demonstrate evidence of drug accumulation. In a separate study, dalbavancin concentrations in rtical bone 12 h after infusion of a single 1,000-mg intravenous infusion were 6.3 μg/g and 2 weeks later were 4.1 μg/g. A two- se, once-weekly regimen that would provide tissue exposure over the dalbavancin MIC for *Staphylococcus aureus* for 8 weeks, aximizing the initial exposure to treatment while minimizing the frequency of intravenous therapy, is proposed.

A bone penetration study (DUR001-105) done in 30 patients enrolled in six separate cohorts of five patientseach and an extended-duration dosing study

Dalbavancin

Bone and Articular Tissue Infection

- Pharmacokinetic modeling of two Phase I studies



	Day 14 Concentrations
Plasma*	15.3
Synovium†	15.9
Synovial fluid*	6.2
Bone†	4.1
Skin†	13.8

*mcg/mL
†mcg/g

MAYO CLINIC

Dunne MW et al. *Antimicrob Agents Chemother* 2014;59(4):1849-55.

Dalbavancina

-BACTERIEMIA??
-ENDOCARDITIS??

D 2005;40:374-80

Efficacy and Safety of Weekly Dalbavancin Therapy for Catheter-Related Bloodstream Infection Caused by Gram-Positive Pathogens

Issam Raad,[1] Rabih Darouiche,[2] Jose Vazquez,[3] Arnold Lentnek,[4] Ray Hachem,[1] Hend Hanna,[1] Beth Goldstein,[5] Tim Henkel,[5] and Elyse Seltzer[5]

[1]The M. D. Anderson Cancer Center and [2]Veterans Affairs Medical Center, Houston, Texas; [3]Harper University Hospital, Detroit, Michigan; [4]Wellstar/Kennestone Hospital, Marietta, Georgia; and [5]Vicuron Pharmaceuticals, King of Prussia, Pennsylvania

Background. Catheter-related bloodstream infections (CR-BSIs) are associated with substantial mortality, prolongation of hospital stay, and increased cost of care. Dalbavancin, a new glycopeptide antibiotic with unique pharmacokinetic properties that have allowed clinical development of a weekly dosing regimen, possesses excellent activity against clinically important gram-positive bacteria, suggesting utility in the treatment of patients with CR-BSIs.

Methods. A phase 2, open-label, randomized, controlled, multicenter study of 75 adult patients with CR-BSIs compared treatment with intravenous dalbavancin, administered as a single 1000-mg dose followed by a 500-mg dose 1 week later, with intravenous vancomycin, administered twice daily for 14 days. Gram-positive bacteria isolated in this study included coagulase-negative staphylococci (CoNS) and *Staphylococcus aureus*, including methicillin-resistant *S. aureus* (MRSA).

Results. Infected patients who received weekly dalbavancin ($n = 33$) had an overall success rate (87.0%; 95% confidence interval [CI], 73.2%–100.0%) that was significantly higher than that of those who received vancomycin ($n = 34$) (50.0%; 95% CI, 31.5%–68.5%). Adverse events and laboratory abnormalities were generally mild and were comparable for the 2 drugs.

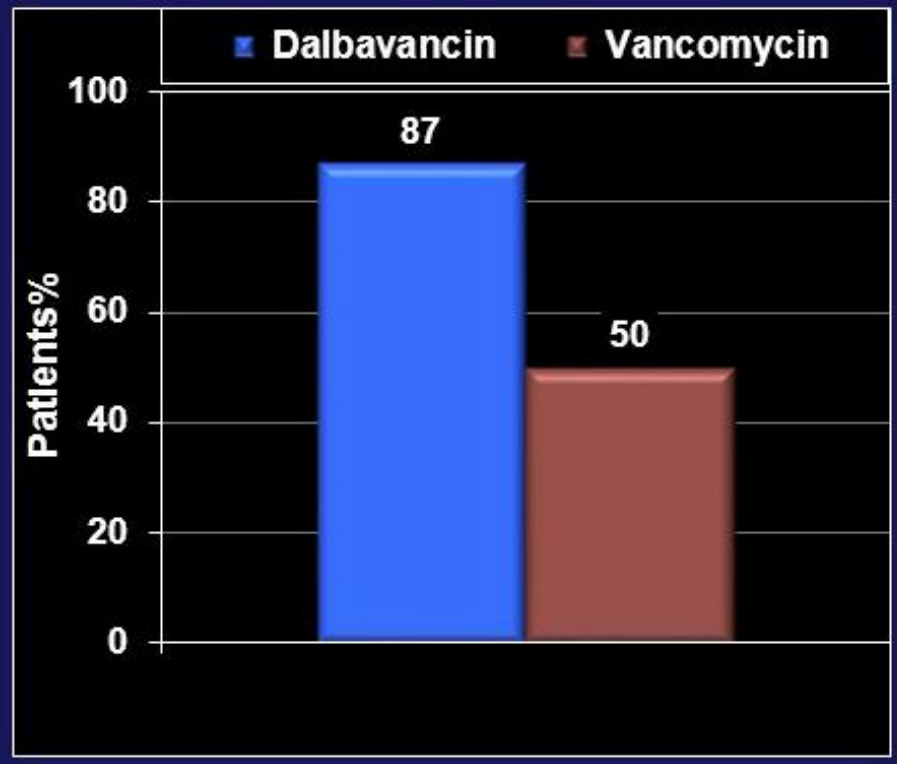
Conclusions. Dalbavancin thus appears to be an effective and well-tolerated treatment option for adult patients with CR-BSIs caused by CoNS and *S. aureus*, including MRSA.

Catheter-Related Bloodstream Infections
Dalbavancin versus Vancomycin

Study Design

- Methods (N 75)
  - Phase 2, randomized, controlled
  - Patients with catheter-related BSI
  - Randomized, open-labeled
  - Catheter-related BSI cause by Gram+
  - Catheters removed for MSSA & MRSA
  - MRSA identified in 51% of patients
- Regimens
  - Dalbavancin: 1.0 g IV d1; 0.5 g IV d8
  - Vancomycin: 1g bid IV x 14d

Overall Success Rate



Source: Raad I, et al. Clin Infect Dis 2005;40:374-80.

Dalbavancin

Catheter-Related Bloodstream Infection

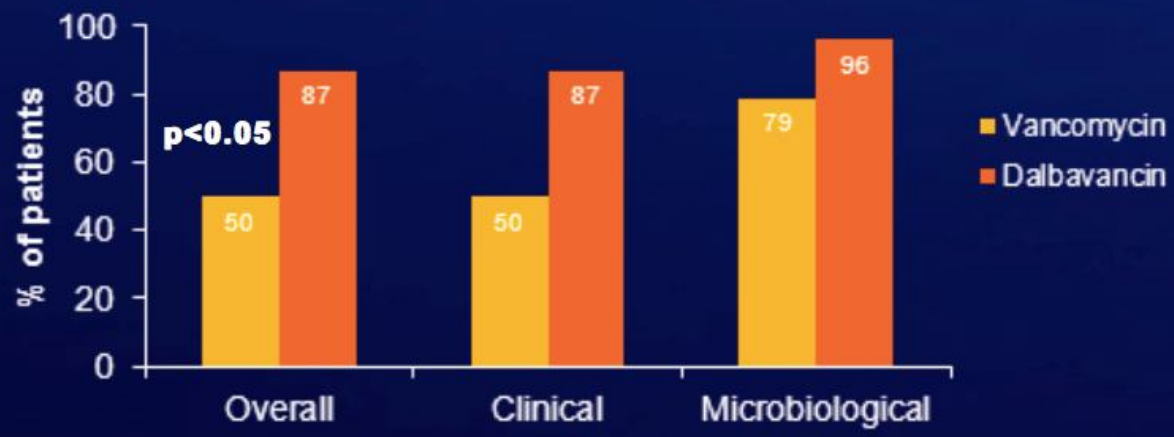
Open-label, randomized, controlled, phase 2 trial

Adults with signs of bacteremia possibly/definitely associated with a catheter

Dalbavancin 1000mg IV day 1 then 500mg IV day 8

Vancomycin 1000mg IV q12h

Success at Test-of-Cure Visit



MAYO CLINIC

MRSA = Methicillin-Resistant *S. aureus*
MSSA = Methicillin-Sensitive *S. aureus*
CoNS = Coagulase-negative *Staphylococcus*

Raad I et al. *Clin Infect Dis* 2005;40(3):374-80.

MID Vienna, Austria 22 – 25 April 2017
ESCMID

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eP 0175

EARLY CLINICAL EXPERIENCE WITH DALBAVANCIN IN A TERTIARY HOSPITAL OF MADRID, SPAIN

Antonio Vena, Maricela Valerio, Patricia Muñoz, Ana Álvarez-Uría, Víctor José González Ramallo, María Eugenia Sánchez Leoni, Carmen Rodríguez González and Emilio Bouza
HOSPITAL GENERAL UNIVERSITARIO GREGORIO MARAÑÓN, MADRID (SPAIN)

Hospital General Universitario Gregorio Marañón
SaludMadrid
Comunidad de M
FEDER
"Una manera de hacer Europa"

NTRODUCTION

ancin (DAL) is a newly approved robial agent for the treatment of acterial skin and soft tissue ns (SSTI) caused by Gram- e microorganisms including llin susceptible (MSSA) and t (MRSA) *S. aureus*, *coccus* spp, *Enterococcus spp and* se negative staphylococci.

dies have reported safety and of patients treated with DAL in nical practice and information ng non-FDA-labeled indications is arcer.

rpose of this study was to report ical experience with DAL in our rtiary care institution mainly in el indications.

METHODS

rospective study included all atients who received at least 1 DAL from January 2016 to ber 2016 at our institution.

mary objective was to describe of DAL in clinical practice, as the outcome and tolerability of nt. We also tried to evaluate the al impact on reduction of length ital stay and costs after DAL tration (considering an ed cost of €325.01 for one day of lisation in an internal medicine Spain).

RESULTS

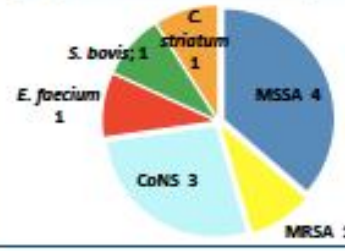
A total of 8 patients received DAL during the study period (75 % male, median age 58), all of them as a targeted therapy (Table 1).

Table 1. Baseline patients' characteristics, previous treatments and dalbavancin treatment information

Characteristics	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8
Age (years)	75	58	57	69	58	38	40	54
Sex	Female	Male	Male	Female	Male	Female	Male	Male
Department	Cardiology	Gastroenterology	Nephrology	Cardiovascular surgery	Vascular surgery	Internal Medicine	Orthopaedics/ Traumatology	Orthopaedics Traumatolog
Underlying disease	Diabetes mellitus Cardiovascular disease	Solid organ malignancy Child B cirrhosis	Diabetes Cardiovascular disease Hemodialysis	Cardiovascular disease	Diabetes mellitus	Cardiovascular disease	Neurological disorder HIV	Neurological Solid organ
Charlson comorbidity index	2	7	6	3	3	2	3	9
Infection type	Pacemaker infection	Prosthetic joint infection	ABSSSI	ABSSSI	ABSSSI	Prosthetic valve IE	Osteomyelitis	Prosthetic jo
Causative microorganism	MSSA	CoNS	MRSA	MSSA CoNS	MSSA	*Streptococcus bovis*	MSSA *Enterococcus faecium*	CoNS
Prior antibiotic therapy	Meropenem Vancomycin	Aztreonam, Vancomycin Daptomycin, Linezolid	Ceftriaxone Vancomycin Daptomycin	Levofloxacin Clindamycin Vancomycin	Amoxicilin clavulanate Ciprofloxacin	Vancomycin Ceftriaxone Gentamicin	Piperacilin tazobactam Daptomycin, Levofloxacin, Cotrimoxazole	Telcoplanin
Prior antibiotic length	2 days	64 days	24 days	7 days	21 days	102 days	25 days	18 days
Main reasons for dalbavancin use	Easier administration	Easier administration Linezolid- induced trombopenia Daptomycin induced eosinophilic pneumonia	Renal failure Resistance to other antibiotics	Easier administration Resistance to other antibiotics	Easier administration Renal failure Interactions	Easier administration	Easier administration Poor adherence	Previous anti
Dose and length	1g day 1, 0.5g day 8	1.5 g day 1	1.5g day 1	1 g, 0.5g day 8	1.5 g day 1	1.5g, 11 doses	1g day 1+ 4 doses 0.5 g	1g day 1, 5
Adverse events	None	None	None	None	None	None	None	None
Outcome	Favorable	Favorable	Favorable	Favorable	Favorable	Favorable	Favorable	Required pro antibiotic su

Abbreviations: ABSSSI: acute bacterial skin and skin structure infections, CoNS: Coagulase negative *Staphylococcus*, HIV: human immunodeficiency virus, IE: infective endocarditis MSSA: meticillin-susceptib *Staphylococcus aureus*, MRSA: meticillin-resistant *S. aureus*.

Fig 1. Causative microorganisms



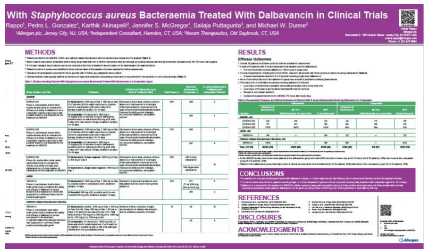
❖ The median DAL administration doses was 4, corresponding to a median of 29 days of DAL exposure. Considering a hy length of hospital stay with other antimicrobial agents of 71.6 days per patients, DAL reduced the total days of hospitali 154 days (26 days per patients), with total saving of about € 50.050.

CONCLUSIONS

- Our study suggests that DAL is a well-tolerated and effective drug for treatment of severe Gram-positive infections.
- DAL can substantially reduce the length of hospital stay.
- Although additional data are needed, the compassionate use of DAL in our patients was found to be satisfactory.

ECCMID Vienna, Austria 22 – 25 April 2017

The congress of ESCMID



P101 What is hot in Staphylococcus aureus bloodstream infection ?

y: 2b. Severe sepsis, bacteraemia & endocarditis

2017, 12:30 - 13:30

es in patients with Staphylococcus aureus bacteraemia treated wi ncin in clinical trials

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Results: All 39 patients (100%) who received dalbavancin (including 8 patients on the single-dose regimen) had clearance of bacteraemia compared with 19/20 (95%) patients treated with comparators (vancomycin or linezolid). For dalbavancin-treated patients, 33/37 (89%) patients were clinical successes at EOT vs 18/23 (78%) patients treated with comparators.

Table 1. Documented Clearance and Clinical Outcomes in *S. aureus* Bacteraemia (Phase 2/3 Studies)

Infection Study	Dalbavancin		
		48–72 h	EOT
	Clearance of Bacteraemia*	≥20% Reduction in Lesion Size	Clinical Success†
ABSSSI, n/N			
DUR001-301	3/3	3/4	2/3
DUR001-302	7/7	9/12	5/6
DUR001-303	15/15	14/15	14/15
cSSSI, n/N			
VER001-9	4/4	–	3/4
Catheter-related bloodstream infection, n/N			
VER001-4	10/10	–	9/9
Total, n/N (%)	**39/39 (100)**	**26/31 (84)**	**33/37 (89)**

ABSSSI=acute bacterial skin and skin structure infection; cSSSI=complicated skin and skin structure infection; EOT=end of treatment. *Patients with follow-up blood culture (post-baseline); †Clinically evaluable population (those with missing data excluded from analysis) of patients with a positive blood culture at baseline.

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Ongoing Clinical Trials

- Dalbavancin
  - Safety and efficacy in adults with osteomyelitis
  - Adults with community-acquired bacterial pneumonia*
  - Children with ABSSSI, osteomyelitis