New Anti-Gram Positive Drugs

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Topics:-

Excluding new agents for *Clostridium difficile* infection

- Overview of marketed and in Phase 3 development
- MICology
- Pharmacokinetics/dynamics
- Clinical trials and other data
- Summary of positives/negatives
- Conclusions

New Anti-Gram Positive Drugs – recently approved by EMA

Name (Sponsor)	Date approved by EMA	Indications
Dalbavancin (Actavis)	2014	Acute bacterial skin and soft tissue infection (ABSSTI)
Oritavancin (The Medicines Co)	2014	ABSSTI
Tedizolid (Merck)	2014	ABSSTI
Ceftobiprole (Basilea)	2013	Pneumonia (community, hospital, excluding ventilator)
Ceftaroline (Pfizer, AZ)	2012	ABSSTI CAP
Telavancin	2011	HAP/VAP due to MRSA

New Anti-Gram Positive Drugs – Phase 3, under review by EMA (Pew Charitable Trust, Update 10/2016)

Name (Sponsor)	Gram-positive pathogens Targeted	Proposed indications
Delafloxacin (Melinta)	S.aureus B.haemolytic streptococci	ABSSTI
Solithromycin (Cempra)	S.pneumoniae	CAP
Eravacycline (Tetraphase)	(S.aureus) (B.haemolytic streps) (Enterococci)	cIAI cUTI
Lefamulin (Nabriva)	S.pneumoniae S.aureus B.haemolytic streps	CAP ABSSTI
Omadacycline (Paratek)	S.pneumoniae (S.aureus) (B.haemolytic streps) (Enterococci)	CAP cIAI cUTI
Fusidic acid (Cempra)	S.aureus B.haemolytic streps	ABSSTI

For further consideration:-

New Agents	Comparators
Dalbavancin Oritavancin (Televancin)	Vancomycin Teicoplanin
Tedizolid	Linezolid
Ceftobiprole Ceftaroline	Cefotaxime

MICs: dalbavancin; oritavancin; telavancin; vancomycin; teicoplanin

	Range	mg/L MIC_{50}	mg/L MIC_{90}	EUCAST wild type cut off
S.aureus (MSSA equivalent to MRSA)				
Dalbavancin	0.008-2	0.03	0.06	≤0.12
Oritavancin+P80	0.008-0.25	0.03	0.06	≤0.12
Telavancin-P80	0.06-1	0.25	0.5	≤1
Telavancin+P80	0.016-0.06	0.03	0.06	-
Vancomycin	0.06-≥128	1	1	≤2
Teicoplanin	0.25-4	0.5	1.0	≤2
Group A Streptococci				
Dalbavancin	0.002-0.25	0.016	0.016	≤0.03
Oritavancin+P80	0.002-0.25	0.03	0.06	≤0.25
Telavancin-P80	0.008-0.12	0.03	0.06	-
Telavancin+P80	0.015-0.06	0.016	0.06	-
Vancomycin	0.06-1	0.5	0.5	≤1
Teicoplanin	0.015-0.25	0.12	0.25	≤0.5

MICs (continued)

	Range	mg/L		EUCAST wild type cut off
		MIC_{50}	MIC_{90}	
E.faecalis				
Dalbavancin	0.016-16	0.03	0.06	≤0.06
Oritavancin +P80	0.002-1	0.016	0.06	≤0.06
Telavancin -P80	0.016-32	0.5	1	-
Telavancin +P80	0.016-4	0.12	0.12	-
Vancomycin	0.12-≥512	2	2	≤4
Teicoplanin	0.03-≥512	0.5	1	≤2
E.feacalis - non vancomycin susceptible				
Dalbavancin Van A	≤0.03-4	≥4	≥4	-
Dalbavancin VanB	≤0.03-4	0.12	4	-
Oritavancin +P80 Van A	0.015-0.5	0.25	0.5	-
Oritavancin +P80 Van B	0.015-0.06	0.015	0.015	-
Telavancin Van A	32-≥128	≥128	≥128	
Telavancin Van B	0.5-1	-	-	

Biedenbach et al, 2009; Mendes et al, 2011; Krause et al, 2008; Draghi et al, 2008

MICs, tedizolid, linezolid

	Range	mg/L		EUCAST wild type cut off
		MIC_{50}	MIC_{90}	
S.aureus (MSSA & MRSA)				
Tedizolid	0.016-16	0.25	0.5	-
Linezolid	0.064-32	2	2	≤4
Group A Streptococci				
Tedizolid	0.016-0.5	0.12	0.25	-
Linezolid	0.064-4	1	2	≤2
E.faecalis				
Tedizolid	0.016-8	0.25	0.5	-
Linezolid	0.12-32	1	2	≤4

Tedizolid 4-8x more active than linezolid against *Strep pneumoniae*

Tedizolid activity against linezolid resistant Staphylococci and Enterococci

Linezolid resistance MIC ≥8mg/L	Range(s)	MIC_{50}	MIC_{90}	Bp
Coagulase Negative (164)	0.06-16	4	8	≤0.5
Staphylococci S.aureus (5)	-	0.5	0.5	≤0.5
27 Linezolid resistant staphylococci and Enterococci Tedizolid MICs ≥1mg/L				

Rodriguez-Avid et al 2012; Toro et al, 2016

MICs: ceftaroline, ceftobiprole; cefotaxime

	Range	mg/L MIC_{50}	mg/L MIC_{90}	EUCAST wild type cut off
MSSA				
Ceftaroline	0.064-2	0.25	0.25	≤0.5
Ceftobiprole	0.03-2	0.25	0.5	≤1
Cefotaxime	0.008-4	2	4	≤4
MRSA				
Ceftaroline	0.03-8	0.25	1	-
Ceftobiprole	0.12-16	1	2	-
Cefotaxime	≥16	≥16	≥16	
Group A Streps				
Ceftaroline	0.004-0.016	0.004	0.004	-
Ceftobiprole	0.004-0.032	0.008	0.016	≤0.03
Cefotazime	0.004-0.25	0.008	0.016	≤0.06
E.faecalis				
Ceftaroline	0.5-8	2	4	-
Ceftobiprole	0.03-64	0.5	2	-
Cefotaxime	0.25-≥64	≥64	≥64	-
S.pneumoniae				
Ceftaroline	0.002-2	0.016	0.125	≤0.03
Ceftobiprole	0.002-4	0.03	0.5	≤0.03
Cefotaxime	0.002-16	0.016	0.064	≤0.064

E.faecium ceftobiprole MIC_{50} 16mg/L, ceftaroline MIC_{50} ≥16mg/L

MICs: Ceftaroline, Ceftobiprole, Penicillin, Amoxicillin, Ceftriaxone

	mg/L		
	Range	MIC_{50}	MIC_{90}
S.pneumoniae		MDR strains (n=260)	
Ceftaroline	0.12-0.5	0.12	0.25
Ceftobiprole	0.25-2	0.5	1.0
Ceftriaxone	0.25-8	2	2
Penicillin	2-8	4	4
S.pneumoniae		PEN MIC>4mg/L (n=221)	
Ceftaroline	0.12-0.5	0.25	0.25
Ceftobiprole	0.25-2	0.5	1.0
Ceftriaxone	0.25-8	2	2

Patel et al, 2009

Pharmacokinetics: Dalbavancin; Oritavancin; Telavancin; Teicoplanin

	Dalbavancin	Oritavancin	Telavancin	Teicoplanin
Doses	1500mg single or 1000mg DI+ 500mg D8	1200mg single	10mg/kg/day	6mg/kg/day (varies)
Cmax (mg/L)	1500mg 411 ± 86 1000mg 281 ± 52 500mg 141 ± 26	138 ± 32	108 ± 26	70 approx
t½(h) (terminal)	372	245 ± 365	8	106-170
AUC (mg/L.h)	0-D14 1 dose 20300	0-inf 2800	0-24h 780	-
Protein binding (%)	93	85	90	87.6-90.8
Excretion	Urine faeces	<5% in urine or faeces	75% urine	80% urine
Renal dose adjustment	Yes	No	Yes[+]	Yes
TDM	No	No	No	Yes

[+]contra-indicated if creatinine clearance ≤30ml/min

Pharmacokinetics: Tedizolid; Linezolid

	Tedizolid	Linezolid
Doses	200mg OD IV or po	600mg BD IV or po
Cmax (mg/L) IV Cmax (mg/L) po	3.0 ± 0.7 2.2 ± 0.7	15.1 ± 2.5 21.2 ± 5.8
t½(h)	12	6
AUC_{24} (mg/L.h) IV AUC_{24} (mg/L.h) po	29.2 ± 6.2 25.6 ± 8.5	179.4 ± 62 214 ± 82
Protein binding (%)	70-90	30
Excretion	Non-renal Sulphate conjugate via liver	Non-renal Breakdown, urine as metabolites
Renal dose adjustable	No	No
Rifampicin Interaction	No interaction in rat model	Cmax ↓21% AUC ↓32%

Pharmacokinetics: Ceftaroline; Ceftobiprole; Cefotaxime

	Ceftaroline	Ceftobiprole	Cefotaxime
Doses	600mg by 60 min infusion 12hrly IV (8hrly also trialled)	500mg by 120 min infusion 8hrly IV	2000mg by 5 min bolus 8hrly IV
Cmax(mg/L)	22.3 ± 5.9	33.0 ± 4.8	176 ± 44
t½(h)	2.5	3.3	0.9
CL (L/h)	12 ± 3.3	5 ± 0.6	-
AUC (mg/L.h)	53.0 ± 123	102 ± 11.9	80 ± 21
Protein binding (%)	20	16	35-64
Excretion	Renal	Renal	Renal
Renal dose adjustment	Yes	Yes	Yes

Pharmacodynamics: Dalbavancin; Oritavancin; Telavancin

	Dalbavancin	Oritavancin	Telavancin
Pattern of bacterial kill (S.aureus)	Bactericidal	Bactericidal	Bactericidal but strain differences
PD driver	fAUC/MIC or fCmax/MIC	AUC, Cmax or T>MIC	fAUC/MIC
Size	200-300 for -1 -2 log kill	Varies with model	40-50 for -1 log drop
Issues	Outside normal paradigm Little clinical data	Outside normal paradigm Clinical data favours large infrequent doses	Little clinical data

Bowker et al, 2006; Andes and Craig, 2007; Boylan et al, 2003; Bowker et al, 2013; Ambrose et al, 2012; MacGowan et al, 2010

Pharmacodynamics: Tedizolid

fAUC/MIC pharmacodynamic driver - as with Linezolid fAUC/MIC 24h static effect 20, -1 log kill 35-45.

WBC increase tedizolid activity markedly.

Lepak et al, 2012; Drusano et al, 2011

Impact of Dose - Phase 2 Trials

	Dose (mg)		
	200	300	400
Modified intention to treat			
End of therapy	92.3 (26)	100 (25)	93.1 (29)
Test of cure	88.5 (26)	100 (25)	89.7 (29)
Clinical evaluable groups similar			

Lodise & Drusano, 2013

Pharmacodynamics: Ceftaroline; Ceftobiprole

	Ceftaroline	Ceftobiprole
Pattern of bacterial kill (S.aureus)	Bactericidal	Bactericidal
PD driver	fT>MIC	fT>MIC
Size of driver (24h) Static - 1 log kill - 2 log kill	 24 ± 9 28 ± 10 29 ± 6	 21 ± 4 - 29 ± 5
Breakpoints	Monte Carlo simulations using a T>MIC target of 36% support a breakpoint of ≤2mg/L EUCAST bp ≤1mg/L	Clinical PK-PD study in cSSSI indicated T>MIC ≥30% or ≥50% related to cure supports a breakpoint of ≤4mgL EUCAST bp ≤2mg/L

MacGowan et al, 2013; Van Wart et al, 2014; Andes & Craig, 2006; Craig & Andes, 2008; Kimko et al, 2009

Safety

Analysis of the Phase 3 ESTABLISH Trials of Tedizolid versus Linezolid in ABSSI: Most common Treatment-Emergent Adverse Events (TEAE)

	Number (%) With TEAE	
	200mg Tedizolid OD	600mg Linezolid BD
Total numbers	662	662
GI disorders (Nausea and vomiting less)	106 (16)	152 (23) p<0.05
Infections	91 (13.7)	78 (11.8)
CNS disorders (Headache, dizziness)	65 (9.8)	67 (10.1)
Skin disorders (Pruritus)	47 (7.1)	40 (6.0)
General disorders (Fatigue)	36 (5.4)	39 (5.9)
Psychiatric disorders (Insomnia)	17 (2.6)	12 (1.8)

Shorr et al, 2014

Safety 2
Analysis of Phase 3 ESTABLISH trials of Tedizolid versus Linezolid in ABSSI

Haematology	Tedizolid	Linezolid
Platelet count ≤150,000 cell/mm^3 at D5-7	3.7%	5.6%
	p = 0.0585	
End of treatment D11-13	4.9%	10%
	P = 0.003	
Neutrophil count lower than lower limit of normal at D5-7	1.7%	2.8%
End of treatment D11-13	1.0%	3.3%
Haemoglobin count lower than lower limit of normal at D5-7	29.4%	33.4%
End of treatment D11-13	28.9%	31.1%

Few patients had toxicity grade shifts in cell lines

Shorr et al, 2014

EMA approved therapeutic indications

	ABSSSI	CAP	HAP excluding VAP	HAP[+] including VAP known or suspected MRSA
Dalbavancin	✓	x	x	x
Oritavancin	✓	x	x	x
Telavancin	x (✓FDA)	x	x	✓
Tedizolid	✓	x	x	x
Ceftaroline	✓	✓	x	x
Ceftobiprole	x	✓	✓	x

[+]if alternatives not suitable

Adding therapeutic detail -
(Scottish Medicines Consortium)

Acute bacterial skin and skin structure infections (ABSSI)

Dalbavancin

- Second line use when MRSA infection suspected or on advice of local infection specialists
- Patient initially in hospital due to ABSSI requiring IV therapy but eligible for early discharge

Tedizolid

- Used specifically in MRSA infection
- Restricted alternative oxazolidinone on advice of local infection specialist

Ceftaroline

- Gram-positive only infection where IV vancomycin not tolerated, inappropriate or treatment modifications required
- Polymicrobial Gram-positive and common Gram-negative infections where IV vancomycin in combination inappropriate, not tolerated, or treatment modifications required.

Hospital acquired pneumonia, excluding VAP

Ceftobiprole

- Use if activity needed against MRSA and Gram-negative pathogens and combination therapy including vancomycin or teicoplanin inappropriate, intolerant or treatment modification needed.

Other potential indications

	Blood Stream Infection	Infective endocarditis	Osteomyelitis
Dalbavancin	Phase 2 study in IV catheter associated Infection	-	On-going trial
Oritavancin	Trial in *S.aureus* blood stream infection case reports in BSI/IE to Enterococci		
Tedizolid	Case reports in Enterococcal bacteraemia	-	On-going trial oral therapy

Raad et al, 2004; Johnson et al, 2015; Bhavnani et al, 2006; Sudhindrfa et al, 2016.

Other indications in literature

	Blood stream infection ± IE (S.aureus Enterococci)	MRSA deep infection including daptomycin non-susceptible	Osteomyelitis/PJI
Ceftaroline	✓[1]	✓[2]	✓
Ceftobiprole	?[3,4]	?	✓

Lin et al, 2012; Ho et al, 2012, Sakoulas et al, 2013; Jongsma et al, 2013; Vazquez et al, 2015; Parsaei et al, 2016; Casapao et al, 2014; Polenakovik and Pleiman 2013; Tattevin et al, 2014

[1] Phase 4 Study of ceftaroline in BSI due to S.aureus or MRSA

[2] Deep infection - muscle, lung, joint, bone

MacDonald and Gow, 2010

[3] Phase 2 Study of ceftobiprole in S.aureus BSI 2007-2013. No enrolment

[4] Trial in neutropenic fever terminated early

Summary

	Dalbavancin	Oritavancin	Telavancin	Tedizolid	Ceftaroline	Ceftobiprole
Known pharma core	++	++	++	++	++	++
Similar agents in development in vitro activity	-	-	-	+	-	-
S.aureus inc MRSA	++	++	++	++	+/++	++
Enterococci inc VRE	+	+/++	+	++	+	+
PK	++	++	-	-	-	-
PD	+	+	++	+	++	+
Resistance concerns	+	+	+/-	+/-	+/-	+/-
Clinical trials	+	+	+	+	+	+
Safety	+	+	-	+	+	+
Other clinical data	+	+	-	+	++	+

Conclusions:-

- Present cohort of "New" anti-gram positive agent represent incremental improvement on existing class members
- All have strength and opportunities

Dalbavancin/Oritavancin

- Infrequent dosing: OPAT, ED use, IE, Osteomyelitis, ABSSTI, line infection

Tedizolid

- Possible improved safety vs linezolid → long term use >28d – Osteomyelitis, IE etc

Ceftobiprole/ceftaroline

- Alternatives for IV therapy, i.e. IE, BSI, Osteomyelitis, Pneumonia due to MRSA

…/cont'd

Conclusions (2)

- All have weaknesses and concerns

Dalbavancin/oritavancin

- Risk of resistance with infrequent dosing/long t½

- Gaps vs glycopeptide resistant strains (VISA, Van A Enterococci)

Tedizolid

- Safety issues

Ceftobiprole/ceftaroline

- Broad spectrum, pharmacore and *C.difficile*
- Clinical breakpoint (Ceftaroline)

- Clear formulary positions – but depends on hospital, economics and logistics