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REVIEW ARTICLE

Renaissance of antibiotics against difficult infections: Focus on oritavancin and new ketolides and quinolones

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Lipoglycopeptide, ketolide, and quinolone antibiotics are currently in clinical development, with specific advantages over available molecules within their respective classes. The lipoglycopeptide oritavancin is bactericidal against MRSA, vancomycin-resistant enterococci, and multiresistant *Streptococcus pneumoniae*, and proved effective and safe for the treatment of acute bacterial skin and skin structure infection (ABSSSI) upon administration of a single 1200 mg dose (two completed phase III trials). The ketolide solithromycin (two phase III studies recruiting for community-acquired pneumonia) shows a profile of activity similar to that of telithromycin, but *in vitro* data suggest a lower risk of hepatotoxicity, visual disturbance, and aggravation of myasthenia gravis due to reduced affinity for nicotinic receptors. Among quinolones, finafloxacin and delafloxacin share the unique property of an improved activity in acidic environments (found in many infection sites). Finafloxacin (phase II completed; activity profile similar to that of ciprofloxacin) is evaluated for complicated urinary tract and *Helicobacter pylori* infections. The other quinolones (directed towards Gram-positive pathogens) show improved activity on MRSA and multiresistant *S. pneumoniae* compared to current molecules. They are in clinical evaluation for ABSSSI (avarofloxacin (phase II completed), nemonoxacin and delafloxacin (ongoing phase III)), respiratory tract infections (zabofloxacin and nemonoxacin (ongoing phase III)), or gonorrhea (delafloxacin).

Key words: *Avarofloxacin, delafloxacin, EDP-322, finafloxacin, oritavancin, nemonoxacin, solithromycin, zabofloxacin*

Key messages

- New antibiotics in the classes of lipoglycopeptides, ketolides, and quinolones are in the late stages of clinical development, mainly for the treatment of acute bacterial infections of skin and skin structures and/or of the respiratory tract.
- These molecules mainly address the problem of resistance in Gram-positive bacteria; their dose has been rationally established based on pharmacokinetic/pharmacodynamic concepts in order to optimize the chance of therapeutic success while at the same time avoiding the risk of selection of resistance.
- They all presented a satisfactory safety profile in clinical trials, which should be further documented upon administration to larger patient populations.

Since the beginning of this century, only 14 new antibiotics have been approved for use in human medicine (Table I). Still-unmet needs include mainly the so-called ESKAPE pathogens (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, *Enterobacter* spp.), which remain difficult to treat because they have accumulated resistance mechanisms to most of the antibiotics available so far. Global initiatives have been raised to try stimulating research and investment in the field of antibiotic development, like the '10 x '20 Initiative' (1) from the Infectious Disease Society of America (http://www.idsociety.org/10x20/) or the 'Innovative Medicine Initiative' (http://www.imi.europa.eu/) from the European Union. At this stage, a series of molecules are in the late stages of clinical development (2,3), many of them being essentially new molecules in existing classes, which display, however, better properties in terms of intrinsic activity, reduced susceptibility to resistance mechanisms, and improved pharmacokinetic or safety profiles. This paper will focus on those families that count molecules in phase III of clinical development, namely lipoglycopeptides (oritavancin), ketolides (solithromycin), and quinolones (nemonoxacin; delafloxacin). It will explain the prevailing rationale in the development of these antibiotics and examine their current pharmacological profile based on available clinical data.

Lipoglycopeptides: focus on oritavancin

Lipoglycopeptides are a subclass within the glycopeptide antibiotics, which all possess a lipophilic tail attached to the amino sugar substituting the cyclic heptapeptide core. Teicoplanin, introduced in the clinics in Europe in 1988, is a natural representative of this subclass. More recently, semi-synthetic derivatives were produced, among which telavancin has been on the market

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Table I. Antibiotics approved by the FDA and the EMA since 2000.

Molecule	Antibiotic class	Date of approval	
		FDA	EMA
Linezolid	oxazolidinone	April 2000	(decentralized procedure; ~ 2001)
cefditoren pivoxil	β-lactam	August 2001	(available in specific countries)
Ertapenem	β-lactam	November 2001	April 2004
Gemifloxacin	fluoroquinolone	April 2003	Not available
Daptomycin	lipopeptide	September 2003	January 2006
Telithromycin	ketolide	April 2004	July 2007
Tigecycline	glycylcycline	2005	April 2006
Retapamulin	pleuromutilin	April 2007	May 2007
Doripenem	β-lactam	October 2007	July 2008
Telavancin	lipoglycopeptide	September 2009	September 2009
Ceftaroline	β-lactam	November 2010	August 2012
Fidaxomicin	fluoroquinolone	May 2011	December 2011
Dalbavancin	lipoglycopeptide	May 2014	Not yet approved
Tedizolid	oxazolidinone	June 2014	Not yet approved

since 2009, dalbavancin has been approved by the FDA in May 2014, and oritavancin is in the late phase of development.

The rationale for the development of these drugs was to cope with vancomycin resistance, which spread in enterococci mainly in the USA at the end of the 1980s.

Vancomycin's mode of action consists in an inhibition of the late stages of peptidoglycan synthesis (4, and references cited herein). The cyclic heptapeptide core of the molecule establishes non-covalent interactions with the D-alanyl-D-alanine termini of the pentapeptide moiety of lipid II. The resulting steric hindrance around these termini prevents the access of enzymes that are needed for cross-linking peptidoglycan precursors via transglycosylation and transpeptidation reactions. As a result, vancomycin is slowly bactericidal, with a spectrum of activity limited to Gram-positive bacteria, because its large size prevents it from crossing the outer membrane of Gram-negative bacteria. Two resistance mechanisms have emerged over the years (4, and references cited herein). The first one, mainly found in enterococci, consists in the acquisition of genes allowing for the synthesis of alternative cell wall precursors ending in D-alanyl-D-lactate or in D-alanyl-D-serine, which show a reduced affinity for vancomycin. At the present time, the prevalence of this resistance mechanism in enterococci collected from infection sites culminates in the USA, reaching 14% (*E. faecalis*) to 88% (*E. faecium*) (5) versus about 10% in Europe but with huge variations among countries (6), 15% in Latin America (7), 2% (*E. faecalis*) to 18% (*E. faecium*) in Canada (8), and, quite surprisingly, low levels of resistance ($<5\%$) in Asia (9). Worryingly, a few cases of gene transfer to multidrug-resistant MRSA (methicillin-resistant *S. aureus*) were reported (13 in the USA and a few in other countries (10), including in important epidemic lineages like US100, US300, and US800). Fortunately, the biological cost of this resistance mechanism is high in MRSA, which may help preventing its spread (11). Another mechanism of resistance emerged in staphylococci, which actually rather confers a moderate level of resistance (VISA phenotype; vancomycin-intermediate *Staphylococcus aureus*). The molecular mechanism thereof is still poorly understood, but it manifests itself by a thickening of the cell wall, in which vancomycin becomes unable to saturate the large number of free D-alanyl-D-alanine termini. These strains are usually cross-resistant to the lipopeptide daptomycin (12), which needs to cross the cell wall to access its target in the bacterial membrane. Heteroresistance to vancomycin is also common in *S. aureus* and corresponds to the presence of subpopulations of bacteria with reduced susceptibility to vancomycin. Heteroresistance or intermediate resistance is associated with higher risk of therapeutic failure (13). The prevalence of these strains is controversial because of the difficulty to detect them correctly.

In this context, early work from Eli Lilly demonstrated that chloroeremomycin, which differs from vancomycin by the stereochemistry of the sugar substituting the ring 4 amino-acid and by the presence of an additional L-4-epi-vancosamine, displayed enhanced activity, including against vancomycin-resistant strains, possibly due to dimerization facilitating a co-operative binding to the target (14). In parallel, derivatives of vancomycin substituted by an alkyl side chain on their vancosamine sugar showed also enhanced activity on resistant strains (15). Combining these two features, oritavancin (initially LY333328; Eli Lilly, Indianapolis, IN, USA) was first described in 1996 (16) as the chlorobiphenylmethyl side chain analog of chloroeremomycin (Figure 1). As compared to vancomycin, this antibiotic shows higher intrinsic activity (lower MICs) (Table II) against susceptible Gram-positive organisms, as well as against staphylococci displaying the VISA phenotype or even against VRE (vancomycin-resisitant enterococci) or VRSA (vancomycin-resistant *S. aureus*) (17,18). This can be explained by a dual mode of action (see for review 19), which combines an inhibition of transpeptidase and transglycosylase activity with an alteration of membrane integrity (20) caused by the anchoring of the lipophilic side chain in the bilayer (21). Importantly also, this novel mode of action confers to oritavancin a rapid and intense bactericidal character, as well as a maintained activity on slow-growing bacteria or on biofilms (22). Among the other remarkable features of this molecule, one should mention its prolonged half-life (terminal half-life >360 h), which can be attributed to both a high protein binding (85%–90%) (4) and an exceptional capacity to accumulate within eukaryotic cells (23), reaching concentrations as high as 560 mg/L in alveolar macrophages of healthy adults having received a cumulative dose of 4 g (24) (Table III). Coupled to the bactericidal character of the drug, this high accumulation confers to oritavancin a high efficacy against intracellular bacteria, including small colony variants of *S. aureus*, which are generally particularly recalcitrant to antibiotic action (25,26).

Oritavancin demonstrated its therapeutic interest in early phase II–III clinical trials, where it proved as effective as comparators for the treatment of complicated skin and soft tissue infections caused by Gram-positive bacteria including MRSA (oritavancin 1.5 or 3 mg/kg once daily for 3–7 days versus 15 mg/kg twice daily for 3–7 days followed by oral cephalexin for up to 10–14 days), and for the treatment of *S. aureus*-associated bacteremia (5–10 mg/kg oritavancin once daily for 10–14

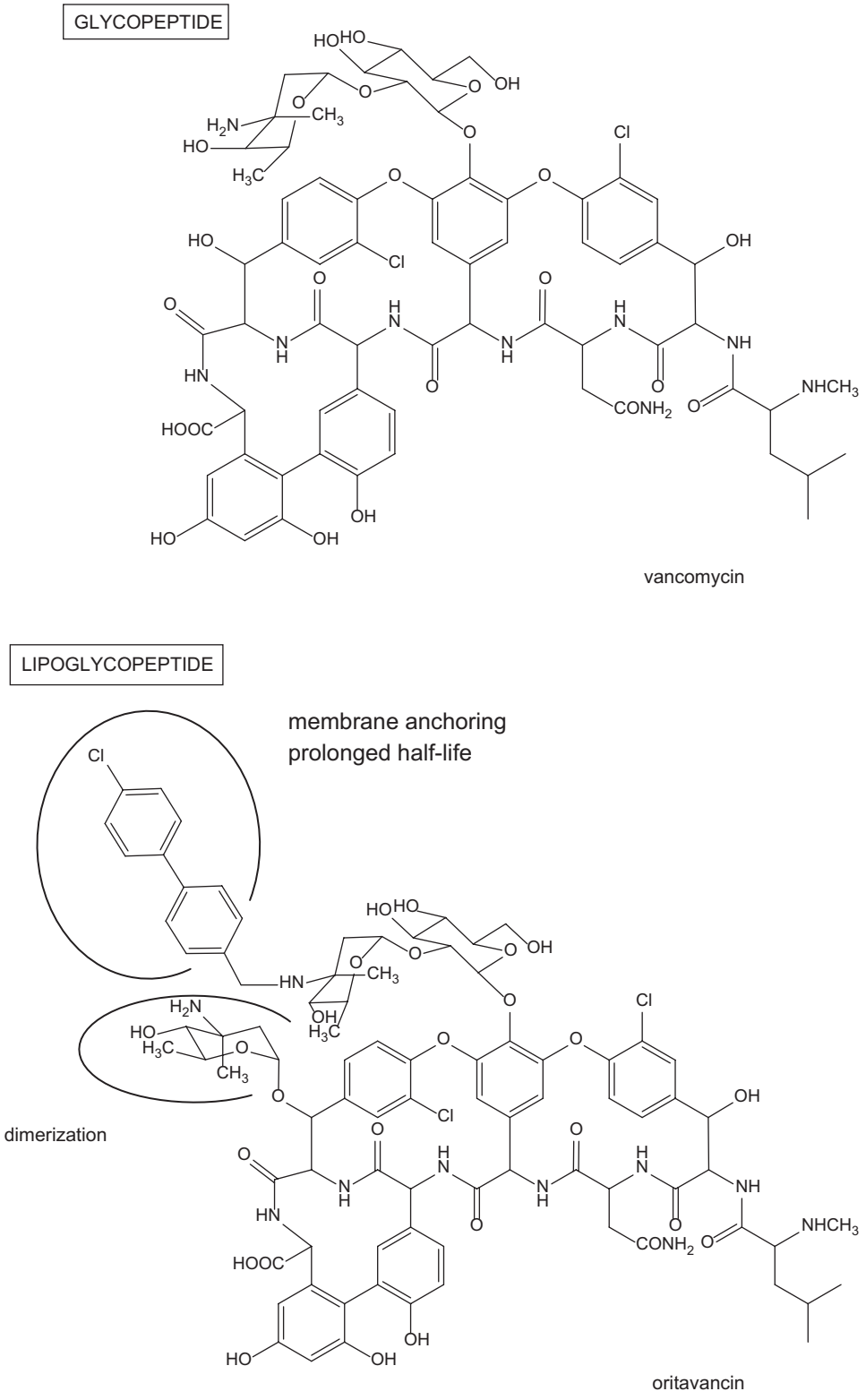

Figure 1. Chemical structure of oritavancin as compared to vancomycin. Major changes are highlighted together with their main consequences for activity or pharmacokinetics.

days versus vancomycin 15 mg/kg twice daily or a beta-lactam for 10–14 days) with no evidence of increased incidence of side effects (see (27) for review). Yet its development was slowed down by successive changes in companies (from Eli Lilly to Intermune Inc., San Francisco, CA (2002), to Targanta Therapeutics Corporation, Montreal, Quebec (2006), to The Medicines Companies, Parsippany, NJ (2009) (28)). A first application to the Food and Drug Administration (FDA) in 2009 was unsuccessful, with a request for an additional phase III trial with more MRSA-infected patients as well as further evaluation of oritavancin effects on macrophage functions, in relation to the huge cellular accumulation of the drug. *In vitro* data documented that the drug could indeed cause a mixed storage disorder in lysosomes (29) as well as inhibition of latex bead phagocytosis (30),

but at concentrations far higher than those observed in alveolar macrophages from treated volunteers. Moreover, no changes in bacterial phagocytosis, killing capacities, or reactive oxygen species production were observed in conditions mimicking human exposure (30,31), ruling out a major risk of toxicity associated to the cellular tropism of the drug. New phase III trials were designed (Table IV), in which the therapeutic scheme was revisited based on recently acquired pharmacodynamic data favoring the administration of a single dose of 1200 mg. The main arguments supporting this unique administration are the concentration-dependent bactericidal character of the drug and its prolonged half-life (32). The corresponding pharmacokinetic data are illustrated in Table III, highlighting a high free C_{max} and prolonged terminal half-life (33). A pilot phase II trial supported this concept (34). It demonstrated that the clinical response was better in patients with acute bacterial skin and skin structure infections treated by a single 1200 mg dose or 800 mg on day 1 followed by 400 mg on day 5 than in those receiving a conventional daily administration of 200 mg for 3–7 days, with no sign of adverse events. Interestingly enough, this therapeutic scheme would be compatible with outpatient parenteral antimicrobial therapy (35,36), which is associated with many benefits (improved quality of life, reduced costs and risks of nosocomial infections). Preliminary reports from these recent phase III studies were released and show equivalent efficacy for a single 1200 mg dose of oritavancin as for a 7–10-day treatment with vancomycin (15 mg/kg BID) (37,38), with no sign of side effects. The US FDA has accepted a new drug application for oritavancin with priority review, with action date scheduled for 6 August 2014. On its side, the European Medicines Agency (EMA) has accepted for review a marketing authorization application in February 2014.

Ketolides: focus on solithromycin

Ketolides are a subclass of macrolide antibiotics characterized by the absence of a 3-O-cladinose sugar (replaced by a keto group), a 11,12- or 6,11-cyclic moiety, and a heteroaryl-alkyl side chain attached to the macrocyclic ring through a suitable linker (39). They show an improved activity against strains resistant to conventional macrolides. Macrolides inhibit protein synthesis by binding to the domain V of the 50S ribosomal subunit and preventing elongation of the peptidic chain. The main mechanism of resistance consists in the methylation of the ribosomal subunit at the position A2058, which considerably reduces the affinity of the antibiotic for its target by creating steric hindrance at the antibiotic binding site. Another mechanism of resistance consists in the expression of efflux systems, which reduce the intrabacterial concentration of the drug. The latter mechanism is responsible for the intrinsic resistance of most Gram-negative bacteria to macrolides and is also associated to acquired, inducible resistance in Gram-positive bacteria, mainly in streptococci. Macrolide resistance is widely spread over the world, reaching 25% in the US (40), 70% in Asia with still higher figures in specific counties (41), and ranging from 50% (Malta) to less than 5% (The Netherlands, Norway, Latvia) in Europe, with intermediate values in most countries (5%–10% in seven countries, 10%–25% in eight countries, and 25%–40% in nine countries) (42). Worryingly also, resistance is emerging and spreading in bacteria responsible for sexually transmitted diseases for which macrolides often represent a first choice (43,44).

By their additional side chain, ketolides bind to both domains V and II of the ribosomal subunit, so that they keep sufficient affinity for methylated ribosomes to inhibit protein synthesis effectively in macrolide-resistant strains. Moreover, the absence of cladinose makes them unable to induce methylase production (45). Ketolides are also less subject to active efflux by *Streptococcus pneumoniae* while remaining extruded by *S. pyogenes* (39,46). Taken together, these properties insured a renewed interest for these antibiotics in the treatment of respiratory tract infections (39). Telithromycin is the only ketolide on the market since 2001 in Europe and 2004 in the US. Yet, its use has been drastically reduced since 2007 because rare but severe side effects were reported, leading to the addition of warnings to the summary of product characteristics (47,48), advising of a risk of acute hepatic failure and severe liver injury, as well as of visual disturbance, transient loss of consciousness, and life-threatening respiratory failure in patients with myasthenia gravis. It has been suggested that these adverse effects could result from a blockade of nicotinic acetylcholine receptors present at the vagus nerve innervating the liver, the ciliary ganglion of the eye, and at the neuromuscular junction, thanks to the pyridine-imidazole group present on the side chain of telithromycin (49).

A series of other molecules are currently in clinical development (Figure 2), which belong to three subfamilies (50), namely 11-N ketolides, including fluoroketolides like solithromycin, 6-O ketolides, such as cethromycin, and bridged bicyclic ketolides like modithromycin (EDP-420) or EDP-322 (developed as its EDP-788 prodrug).

Cethromycin (Abbott compound ABT-773, further developed by Advanced Life Sciences, Inc., Woodridge, IL, USA) completed two phase III trials where it was compared at a dose of 300 mg QD to clarithromycin (250 mg BID) for the treatment of community-acquired pneumonia (51). However, it was denied by the FDA in 2009, being considered as safe but not effective enough to justify its marketing, as it essentially showed equivalence to clarithromycin (52).

The Enanta Pharmaceuticals (Watertown, MA, USA) compound modithromycin entered phase II clinical trials in 2006 but has now been supplanted by EDP-322, which is at the present time in phase I. While modithromycin was essentially studied *in vitro* and *in vivo* as an antipneumococcal drug (53–55), EDP-322 is rather positioned as a potent anti-MRSA agent.

The fluoroketolide solithromycin (CEM-101; Cempra Inc., Chapel Hill, NC, USA) is currently recruiting patients for two phase III clinical trials where it is compared with oral moxifloxacin for the treatment of community-acquired pneumonia. As compared to telithromycin, solithromycin may offer an improved safety profile. Since its side chain does not possess the pyridine-imidazole group of telithromycin, it is a 30-times less potent inhibitor of nicotinic receptors than telithromycin (49). Accordingly, none of the rare adverse effects of telithromycin had been observed in current phase I/II trials with solithromycin (56). With respect to its mode of action, solithromycin, as other ketolides, remains capable of binding to ribosomes that are mono- or even dimethylated, thanks to three structural features. First, the absence of cladinose gives more movement freedom to the desosamine sugar and allows repositioning of the antibiotic in the ribosomal binding site. This avoids the steric clash between the antibiotic and the dimethylated A2058 that explains poor binding of conventional macrolides to dimethylated ribosomes and subsequent resistance. Second, the additional aryl-alkyl side chain can interact with a base pair formed by A752 and U2609 in the 23S RNA from both native and methylated ribosomes, further contributing to strengthen the antibiotic binding to ribosomes from susceptible and resistant strains. Third, the 2-fluorine substituent, which is not present

Table II. Susceptibility of relevant pathogens to antibiotics in development and their comparators.

Species	Phenotype	Antibiotic	MIC_{50} (mg/L)	MIC_{90} (mg/L)	MIC range (mg/L)	Reference [a]
S. aureus	MRSA—all	vancomycin	1	1	≤0.12–2	(18)
			1	1	0.5–2	(143)
				1	≤0.25–2	(144)
		oritavancin	0.03	0.06	≤0.008–0.5	(18)
			0.06	0.12	0.015–0.25	(143)
				0.12	≤0.004–4	(144)
		erythromycin	>2	>2	≤0.25–>2	(145)
			>4	>4	0.25–>4	(65)
		clarithromycin	0.25	>128	0.25–>128	(146)
			>8	>8	≤0.12–>8	(147)
		cethromycin	0.03	0.03	0.015–0.12	(146)
			≤0.002	≤0.002	≤0.002–0.125	(147)
		solithromycin	0.06	>4	0.03–>4	(145)
			0.12	>16	0.03–>16	(65)
		levofloxacin	8	32	0.03–>32	(129)
		moxifloxacin	4	16	0.03–>64	(112)
			0.125	4	0.03–8	(127)
		zabofloxacin	2	4	0.008–32	(112)
		delafloxacin	0.125	0.5	≤0.004–16	(129)
			0.03	0.5	0.008–1	(127)
	hVISA	vancomycin		2	1–2	(148)
		oritavancin		1	0.12–2	(148)
	VISA	vancomycin	4	8	4–8	(143)
				8	4–8	(148)
		oritavancin	1	2	0.25–2	(143)
				2	0.5–4	(148)
		erythromycin	>4	>4	>4	(65)
		solithromycin	>16	>16	0.06–>16	(65)
		nemonoxacin	0.5	2	0.03–8	(149)
	VRSA	vancomycin	>64	>64	32–>64	(143)
		oritavancin	0.5	1	0.25–1	(143)
	MRSA ML-R	erythromycin	>512	>512	>512	(150)
		cethromycin	>64	>64	>64	(150)
	MRSA FQ-S	moxifloxacin	0.06	0.12	0.06–0.25	(116)
			0.06	0.06	≤0.015–0.12	(151)
			0.06	0.06	0.03–0.12	(152)
			0.03/*0.25*[b]	0.125/*0.5*	0.06–0.125/*0.25–0.5*	(101)
		finafloxacin	0.125/*0.06*	0.25/*0.125*	0.125–0.25/*0.06–0.125*	(101)
		zabofloxacin	0.031	0.125	0.016–1	(153)
		avarofloxacin	≤0.008	≤0.008	≤0.008–0.015	(152)
		nemonoxacin	0.03	0.06	≤0.008–0.12	(116)
			0.03	0.06	≤0.008–0.06	(151)
		delafloxacin			0.008–0.03	(154)
	MRSA FQ-R	moxifloxacin	8	16	1–16	(116)
			4	4	0.12–8	(151)
			4	8	0.25–>16	(155)
			4	>16	1–>16	(152)
			2/*8*	32 / *32*	2–32/*0.5–64*	(101)
		finafloxacin	2/*1*	16 / *4*	0.25–32/*0.25–32*	(101)
		zabofloxacin	2	32	0.016–64	(153)
		avarofloxacin	0.25	0.25	0.015–2	(155)
			0.25	1	0.12–4	(152)
		nemonoxacin	0.5	1	0.5–1	(149)
			4	16	0.25–64	(116)
			1	1	0.06–4	(151)
		delafloxacin			0.5–2	(154)
E. faecium	VAN-S	vancomycin		1	0.03–4	(144)
			1	1	0.25–4	(156)
		oritavancin		0.03	≤0.0005–0.25	(144)
			≤0.008	≤0.008	≤0.008–0.03	(156)
		erythromycin	>4	>4	≤0.12–>4	(65)
		solithromycin	0.25	2	0.03–2	(65)
		nemonoxacin	4	4	0.06–8	(149)
	VAN-R	vancomycin	≥64	≥64	8–>256	(17)
				>256	>256	(144)
			>16		>16	(156)
		oritavancin	0.015	0.06		(17)
				0.25	≤0.0005–1	(144)
			0.03	0.06	≤0.008–0.25	(156)
		erythromycin	>4	>4	0.25–>4	(65)
		solithromycin	2	2	0.25–2	(65)
		nemonoxacin	4	16	0.06–16	(149)
S. pneumoniae	all	vancomycin		0.25	≤0.06–0.5	(144)

(*Continued*)

Table II. (*Continued*)

Species	Phenotype	Antibiotic	MIC_{50} (mg/L)	MIC_{90} (mg/L)	MIC range (mg/L)	Reference [a]
		oritavancin		0.008	≤0.0005–0.5	(144)
		clarithromycin	0.06	>128	0.03–>128	(146)
			0.25	64	0.004–64	(72)
		cethromycin	0.015	0.12	0.008–16	(146)
		solithromycin	0.015	0.06	0.002–1	(72)
		moxifloxacin	0.12	0.25	0.008–>8	(105)
			0.5	1	0.125–0.5	(101)
		finafloxacin	1	2	0.5–4	(101)
		zabofloxacin	0.015	0.03	0.015–0.06	(112)
			0.063	1	0.008–4	(153)
		avarofloxacin	0.008	0.015	≤0.004–1	(105)
	S	moxifloxacin	0.12	0.25	0.03–0.25	(157)
			0.12	0.12	0.06–0.25	(151)
			0.5	0.5	0.125–0.5	(112)
		zabofloxacin	0.016	0.03	≤0.001–0.06	(157)
			0.015	0.03	0.015–0.06	(112)
		nemonoxacin	0.12	0.12	0.06–0.25	(151)
	Pen-R	vancomycin		0.25	0.25–0.5	(144)
		oritavancin		0.008	0.002–0.015	(144)
		moxifloxacin	0.12	0.25	0.03–0.25	(157)
			0.12	0.25	0.06–0.25	(116)
		zabofloxacin	0.016	0.03	0.004–0.03	(157)
		nemonoxacin	0.015	0.015	0.015–0.06	(116)
	ML-S	erythromycin	0.062	0.125	0.015–0.125	(150)
		clarithromycin	0.03	0.06	0.015–0.06	(158)
		cethromycin	≤0.007	0.031	≤0.007–0.31	(150)
		solithromycin	0.008	0.015	0.002–0.015	(158)
	ML-R	vancomycin		0.5	0.12–0.5	(144)
		oritavancin		0.25	0.008–0.5	(144)
		erythromycin	64	>128	1–>128	(150)
		clarithromycin			1–>64	(158)
		cethromycin	0.031	0.25	≤0.007–2	(150)
		solithromycin			0.015–1	(158)
	FQ-R	moxifloxacin	2	4	2–8	(157)
			2	8	2–>8	(151)
			1	16	4–16	(155)
			4	8	0.25–>8	(105)
E. coli	all	ciprofloxacin	0.015	0.5	0.008–64	(112)
			0.063	0.5	0.008–8	(153)
			0.06	16	0.06–16	(116)
		zabofloxacin	0.06	1	0.015–64	(112)
			0.125	0.5	0.008–32	(153)
		nemonoxacin	0.12	32	≤0.015–≥512	(116)
	FQ-S	ciprofloxacin	0.016/*0.125*	0.03/*0.25*	≤0.008–0.125/*0.06–2*	(101)
			0.015	0.25	0.08–0.25	(154)
					0.008–2	(155)
		finafloxacin	0.125/*0 .016*	0.25/*0.03*	0.03–1/≤*0.008–0.125*	(101)
		avarofloxacin	0.06	0.25	0.015–0.5	(155)
		delafloxacin			0.016–0.25	(154)
	FQ-R	ciprofloxacin	128 / >*256*	>256 / >*256*	8–>256 / >*256*	(101)
			64	256	64–>128	(154)
					16–>256	(155)
		finafloxacin	128 / *8*	256 / *32*	164–>256 / *2–64*	(101)
		avarofloxacin	4	16	1–16	(155)
		delafloxacin			2–128	(154)
Enterobacter spp.		ciprofloxacin	≤0.03/*0.125*	≤0.03/*0.25*	≤0.03 / *0.06–0.5*	(101)
		finafloxacin	0.125/≤ *0.03*	0.125/≤ *0.03*	0.06–0.5/≤*0.03–0.125*	(101)
P. aeruginosa	all	ciprofloxacin	0.25	2	0.002–16	(153)
			0.5	16	0.06–16	(116)
			0.25	0.5	0.125–1	(155)
		zabofloxacin	1	32	0.016–64	(153)
		nemonoxacin	1	32	0.12–≥512	(116)
		avarofloxacin	1	2	0.5–4	(155)
	FQ-S	ciprofloxacin	0.25/*0.5*	0.5 / *1*	0.03–1/*0.125–2*	(101)
					0.25–2	(154)
		finafloxacin	1 / *0.5*	32 / *2*	4–16 / *0.25–8*	(101)
		delafloxacin			0.016–1	(154)
	FQ-R	ciprofloxacin			64–>128	(154)
		delafloxacin			4–32	(154)

S = susceptible; FQ-R = fluoroquinolone-resistant; FQ-S = fluoroquinolone-susceptible; hVISA = heterogenous vancomycin-intermediate *S. aureus*; ML-R = macrolide-resistant; ML-S = macrolide-susceptible; MRSA = methicillin-resistant *S. aureus*; Pen-R = penicillin-resistant (based in most cases on CLSI = (Clinical and Laboratory Standards Institute) susceptibility breakpoints for marketed comparators); VISA = vancomycin-intermediate *S. aureus*; VRSA = vancomycin-resistant *S. aureus*.

[a]Comparison of MIC distributions among antibiotics should be performed using data from the same bibliographic reference.

[b]Values in italics: MICs determined at acidic pH (~5.2).

in telithromycin, may possibly account for the higher intrinsic activity of solithromycin as compared to telithromycin (57). As for other macrolides and ketolides, solithromycin's pharmacokinetic profile is characterized by a broad tissue distribution and high cellular accumulation (58,59), reaching elevated concentrations in alveolar macrophages (24-h AUC: 1500 mg.h/L; ratio to serum concentration: 180) and epithelial lining fluid (24-h AUC: 80 mg.h/L; ratio to serum concentration: 10). Its half-life of 6.65 h related to a high protein binding (85%) (60) allows for a once-a-day administration, with a proposed therapeutic scheme by oral route consisting in a loading dose of 800 mg followed by a 4-day treatment with a daily dose of 400 mg. In these conditions, serum levels reached a C_{max} and an AUC of approx. 0.8 mg/L and 7 mg.h/L (for a 400 mg dose) (Table III) and of approximately 1.3 mg/L and 14 mg.h/L (for an 800 mg dose) (60). This scheme allows reaching the pharmacodynamic target demonstrated as predictive of efficacy for this drug, namely an AUC/MIC $>$ 1.3 h in epithelial lining fluid (ELF) (61) with a probability of 99.9% for MICs as high as 1 mg/L (62). However, a loading dose does not seem necessary when administering the drug by intravenous route (63). MIC_{90} against contemporary isolates of respiratory pathogens were 0.25 mg/L for *S. pneumoniae* (0.5 mg/L for multiresistant strains), 0.015 mg/L for *Legionella pneumophila*, and 0.5 mg/L for *Moraxella catarrhalis*. As other macrolides, solithromycin is less active on *Haemophilus influenzae* (MIC_{90} 2 mg/L). Nevertheless, all MIC_{90} values remain lower than those recorded for telithromycin (64). Solithromycin also shows useful activity against staphylococci and enterococci (65), or pathogens causing sexually transmissible diseases (*Chlamydia trachomatis* (66), *Neisseria gonorrhoeae* (67–69), *Mycoplasma* spp. (70,71)). Interestingly, solithromycin MICs remain low against strains resistant to conventional macrolides or to other antibiotic classes (72,73), suggesting it may represent a useful alternative to currently recommended drugs in areas with high resistance rates. Lastly, solithromycin demonstrates activity against biofilms formed by *S. pneumoniae* (74), which may be an advantage when dealing with chronic infections where biofilms are thought to play a major role in recurrence of the infection. Taken together, these properties are advantageous for the treatment of respiratory or genital infections. They also rationalize activity against intracellular pathogens like *S. aureus*, *Listeria monocytogenes*, *L. pneumophila*, and *N. gonorrhoeae* (58,67), against which solithromycin proves at least as effective but more potent than other macrolides, based essentially on its lower MICs and not on its higher accumulation level. In the clinics, solithromycin has, at this stage, already proven as effective as levofloxacin with a more favorable safety profile in a phase II trial for the treatment of community-acquired bacterial pneumonia, where patients were randomized to receive either 800 mg solithromycin orally on day 1, followed by 400 mg daily on days 2 to 5, or 750 mg levofloxacin during 5 days (75). Notably, no influence on the QTc interval was observed so far (56). A phase II clinical trial is examining the efficacy of a single dose for the treatment of uncomplicated gonorrhea. The drug has received the Qualified Infectious Disease Product (QIDP) status and Fast Track designation for community-acquired pneumonia from the US FDA in September 2013.

Quinolones

Quinolone antibiotics represent one of the largest antibiotic classes when considering that already in 2005 about 10,000 compounds had been patented and 800 million patients had been treated (76,77). Fluoroquinolones inhibit bacterial replication by forming a ternary complex with DNA and class II topoisomerases (DNA gyrase and topoisomerase IV), two enzymes responsible for DNA supercoiling. Quinolones have been categorized in successive generations (77–79) based on the nature of their substituents, which governs their interaction with their pharmacological target and their spectrum of activity (77,79). The substituents that best increase potency are a cyclopropyl or, alternatively, a difluorophenyl in position 1, a fluorine in position 6, and a halogen, methoxy, or fused third ring in position 8 (Figure 3). Molecules harboring a piperazine-based substituent in position 7 are in general more active on Gram-negative bacteria and preferentially target DNA gyrase, while those presenting a pyrrolidine-based substituent rather show activity on Gram-positive bacteria and target topoisomerase IV. Dual targeting molecules present a broad spectrum of activity. Nalidixic acid (by-product of antimalarial research) is representative of the first generation, with only a narrow spectrum, low serum levels, and toxicity issues. The second generation is characterized by the addition of a fluorine substituent at position 6 (hence the name of fluoroquinolones often given to the whole class), which markedly increases activity. Ciprofloxacin is the most widely used molecule in this generation and remains one of the most active fluoroquinolones on Gram-negative bacteria. Levofloxacin, the active isomer of ofloxacin, another second-generation molecule, is considered by certain authors as constituting an independent generation (78). Moxifloxacin is the leading molecule in the next generation, which is characterized by a spectrum of activity rather oriented towards Gram-positive bacteria including anaerobes (activity on Gram-negative anaerobes like *Bacteroides* is too weak to envision its use for the treatment of intra-abdominal infections (80)). Among more recent generations, one can find molecules like gemifloxacin (marketed in the US and in Korea), which also include Gram-positive anaerobes in their spectrum, or garenoxacin (marketed in Japan), which lacks the fluorine in position 6, giving rise to the desfluoroquinolones subclass (77). Despite the tremendous number of molecules produced, only a few of them were brought on the market, among which some were withdrawn or have seen their use restricted because

Table III. Main pharmacokinetic properties of antibiotics.

Antibiotic	Dose and route	C_{max} (mg/L)[a]	AUC (mg.h/L)[a]	Protein binding (%)	$T_{1/2}$ (h)	Tissue/serum conc. ratio	References
Oritavancin	1200 mg IV	19.4 (free)	132	85	31.3 (β) 393 (γ)	0.03–0.1 (ELF) 1–56 (AM)	(24,33)
Solithromycin	400 mg IV	0.8	7	85	6.6	2.4–28.6 (ELF) 44–515 (AM)	(59,60)
Finafloxacin	800 mg oral	11	28		10		(103)
Avarofloxacin	250 mg oral	2	35	65	14	17–64 (ELF) 74–157 (AM)	(109)
Zabofloxacin	400 mg oral	2	11				(114)
Nemonoxacin	500 mg oral	3.5–5	32	16	10–15		(119,120)
Delafloxacin	300 mg IV	10	24	16	8–12		(132,133)

ELF = epithelial lining fluid; AM = alveolar macrophages.
[a]Total concentration, unless stated otherwise.

Table IV. Recent clinical trials posted on the clinicaltrials.gov repository for antibiotics under development.

Study number and development phase	Drugs and doses	Study title	Status
Oritavancin			
NCT01784536; phase I	Single-dose IV oritavancin diphosphate; dose not specified	Open Label Study Evaluating the Effects of a Single Oritavancin Infusion on Cytochrome P450 in Healthy Volunteers	Completed (2013)
NCT01762839; phase I	Single-dose IV oritavancin diphosphate (single dose 1600 mg); comparators: placebo, moxifloxacin single dose 400 mg	A Study to Assess the Cardiac Safety of Oritavancin in Healthy Volunteers	Completed (2013)
NCT00514527; phase II	Oritavancin single dose (1200 mg), infrequent dose (800 mg at day 1 and 400 mg at day 5); comparator: versus daily dose of oritavancin (200 mg) for 3–7 days	A Study for Patients With Complicated Skin and Skin Structure Infections (SIMPLIFI)	Completed (2008)
NCT01252719; phase III	Single-dose IV oritavancin diphosphate (1200 mg day 1 followed by placebo); comparator: IV vancomycin	Oritavancin Versus IV Vancomycin for the Treatment of Patients With Acute Bacterial Skin and Skin Structure Infection (SOLO I)	Completed (2012)
NCT01252732; phase III	Single-dose IV oritavancin diphosphate (1200 mg day 1 followed by placebo); comparator: IV vancomycin for 7–10 days (dose not specified)	Oritavancin Versus IV Vancomycin for the Treatment of Patients With Acute Bacterial Skin and Skin Structure Infection (SOLO II)	Completed (2013)
EDP-322 / EDP-788			
NCT00989872; phase I	Single ascending dose of EDP-322; comparator: placebo	Safety and Pharmacokinetics of Ascending Single Oral Doses of EDP-322 in Non-fasting and Fasting Healthy Volunteers	Completed (2009)
NCT00990145; phase I	Multiple oral doses of EDP-322 ranging from 200 to 800 mg; comparator: placebo	Multiple Ascending-Dose Study of EDP 322 in Healthy Adult Volunteers	Completed (2009)
NCT01999725; phase I	Single doses with dose escalation to continue in successive cohorts; comparator: placebo	Evaluation of the Safety and Pharmacokinetics of a Single Oral Dose of EDP-788	Not yet recruiting
Solithromycin			
NCT01966055; phase I	Solithromycin; dose not specified	Pharmacokinetics and Safety of Solithromycin Capsules in Adolescents	Recruiting
NCT01168713; phase II	Oral solithromycin (800 mg QD day 1; 400 mg QD days 2–5) ; comparator: oral levofloxacin (750 mg QD days 1–5)	Efficacy and Safety Study of Oral CEM-101 Compared to Oral Levofloxacin in Treatment of Patients With Community-Acquired Bacterial Pneumonia	Completed (2011)
NCT01591447; phase II	Single dose solithromycin 1000 mg by oral route	Safety and Efficacy Study of Single-Dose Oral CEM-101 in Patients With Uncomplicated Urogenital Gonorrhea	Completed (2013)
NCT01968733; phase III	Solithromycin (intravenous with the potential step-down to oral); comparator: moxifloxacin (intravenous with the potential step-down to oral); doses not specified	Efficacy and Safety Study of Intravenous to Oral Solithromycin (CEM-101) Compared to Intravenous to Oral Moxifloxacin in Treatment of Patients With Community-Acquired Bacterial Pneumonia (SOLITAIRE-IV)	Recruiting
NCT01756339; phase III	Solithromycin (800 mg orally on day 1 followed by 400 mg daily on days 2 through 5, followed by placebo on days 6 and 7); comparator: moxifloxacin (400 mg orally on day 1 to 7)	Efficacy and Safety Study of Oral Solithromycin (CEM-101) Compared to Oral Moxifloxacin in Treatment of Patients With Community-Acquired Bacterial Pneumonia (SOLITAIRE-ORAL)	Recruiting
Finafloxacin			
NCT00723502; phase II	Finafloxacin 400 mg BID + amoxicillin 1000 mg BID; finafloxacin 400 mg BID + esomeprazole 40 mg BID in patients with *Helicobacter pylori* infection	Efficacy and Safety Study of Finafloxacin Used in *Helicobacter pylori* Infected Patients	Completed (2009)
NCT01910883; phase I	Dose-escalating study of single and multiple (7 days) oral doses (200–1000 mg) of finafloxacin IV	Safety and Tolerability of Single and Multiple Intravenous Doses of Finafloxacin in Healthy Subjects	Completed (2012)
NCT01907867; phase I	Finafloxacin 800 mg (4 × 200 mg tablet) QD for 3 days	Pharmacokinetic Profile in Plasma and Epithelial Lining Fluid of Finafloxacin	Completed (2012)
NCT01904162; phase I	Single dose of finafloxacin hydrochloride	Effect of Age and Gender on the Pharmacokinetics and Tolerability of Finafloxacin	Completed (2010)
NCT00483158; phase I	Dose-escalating study of single and multiple oral doses of finafloxacin hydrochloride	First Time in Man Study of Finafloxacin Hydrochloride	Completed (2008)
NCT01928433; phase II	Finafloxacin 800 mg (IV or oral) QD; comparator: ciprofloxacin 400 mg IV or 500 mg oral BID	Finafloxacin for the Treatment of Complicated Urinary Tract Infections (cUTI) and/or Acute Pyelonephritis	Recruiting
NCT00722735, phase II	Oral finafloxacin 300 mg BID for 3 days; comparator: oral ciprofloxacin 250 mg BID for 3 days	Finafloxacin 300 mg Twice a Day (BID) Versus Ciprofloxacin 250 mg Twice a Day (BID) in Patients With Lower Uncomplicated UTI (uUTI) (FLUT)	Completed (2009)

(*Continued*)

Table IV. (Continued)

Study number and development phase	Drugs and doses	Study title	Status
Zabofloxacin			
NCT01341249; phase I	Single oral administration in healthy male volunteers of 488 mg zabofloxacin aspartate tablet and 400 mg zabofloxacin hydrochloride capsule	A Study to Compare the Pharmacokinetic Profiles of DW224aa (Zabofloxacin aspartate) and DW224a (Zabofloxacin hydrochloride)	Completed (2011)
NCT01081964;	Zabofloxacin (400 mg orally QD for 3 or 5 days); comparator: levofloxacin (500 mg orally QD for 7 days)	Safety and Efficacy Study of Oral Zabofloxacin in Community Acquired Pneumonia	Completed (2012)
NCT01658020; phase III	Zabofloxacin (400 mg orally QD); comparator: moxifloxacin (400 mg orally QD)	A Study to Evaluate Efficacy and Safety Profile of Zabofloxacin Tablet 400 mg and Moxifloxacin Tablet 400 mg (DW224-III-3) after Multi-dose Oral Administration in Patients With Acute Bacterial Exacerbation of Chronic Obstructive Pulmonary Disease.	Ongoing, not recruiting
Nemonoxacin			
NCT01395108; phase I	Single and multiple ascending oral doses of nemonoxacin	Clinical Study on Oral Nemonoxacin Malate Capsules	Completed (2008)
NCT01529957; phase I	Single and multiple ascending IV doses of nemonoxacin	A Study of Nemonoxacin Malate Sodium Chloride Injection Administered by Intravenous Infusion	Completed (2011)
NCT00434291; phase II	Not provided	Safety and Efficacy Comparison of TG-873870 (Nemonoxacin) to Levofloxacin in Community-Acquired Pneumonia	Completed (2009)
NCT00685698; phase II	Nemonoxacin 750 mg, oral administration, once daily for 7 ± 1 and 14 ± 1 days	Safety and Efficacy Study of TG-873870 (Nemonoxacin) in Diabetic Foot Infections	Completed (2009)
NCT01537250; phase II	Nemonoxacin (750 mg orally 2 tablets or 500 mg orally 3 tablets) ; comparator: levofloxacin (500 mg orally QD + placebo) for 7 days	Study to Assess the Efficacy and Safety of Nemonoxacin Malate in Treating Adult Patients With Community-acquired Pneumonia (CAP)	Completed (2010)
NCT01944774; phase II	Nemonoxacin (500 mg or 650 mg QD IV for 7–14 days); comparator: moxifloxacin (400 mg QD IV for 7–14 days)	Study to Evaluate the Efficacy and Safety of Intravenous Infusion With TG-873870 (Nemonoxacin) Versus Moxifloxacin in Treating Adult Patients With Community Acquired Pneumonia (CAP)	Recruiting
NCT01529476; phase III	Nemonoxacin (500 mg orally); comparator levofloxacin (500 mg orally) for 7–14 days	Study to Evaluate the Efficacy and Safety of Oral Administration With Nemonoxacin and Levofloxacin in Patients With Community-acquired Pneumonia (CAP)	Completed (2012)
Delafloxacin			
NCT00719810; phase II	Delafloxacin (300 mg or 450 mg IV BID); comparator: tigecycline (100 mg on day 1 then 50 mg IV BID)	Safety and Efficacy Study of a Fluoroquinolone to Treat Complicated Skin Infections	Completed (2008)
NCT01283581; phase II	Delafloxacin (300 mg IV BID) for 5–14 days; comparators: linezolid (600 mg IV BID) and vancomycin (15 mg/kg, up to 1250 mg, IV BID) for 5–14 days	A Study to Assess Objective Endpoint Measurements of Response in Bacterial Skin Infections	Completed (2011)
NCT02015637; phase III	Delafloxacin 900 mg orally (2×450 mg) QD; comparator: ceftriaxone (250 mg IM QD)	Comparison of Delafloxacin Versus Ceftriaxone for the Treatment of Uncomplicated Gonorrhea	Recruiting
NCT01811732; phase III	Delafloxacin (300 mg IV BID) for 5–14 days; comparator: vancomycin (15 mg/kg IV) + aztreonam (2 g) BID	Delafloxacin Versus Vancomycin and Aztreonam for the Treatment of Acute Bacterial Skin and Skin Structure Infections	Recruiting
NCT01984684; phase III	Delafloxacin (300 mg IV BID 300 mg iv BID for 3 days) followed by 450 mg oral BID for 5–14 days total; comparator: vancomycin (15 mg/kg IV) + aztreonam (2 g) BID	Delafloxacin vs Vancomycin and Aztreonam for the Treatment of Acute Bacterial Skin and Skin Structure Infections	Not yet recruiting

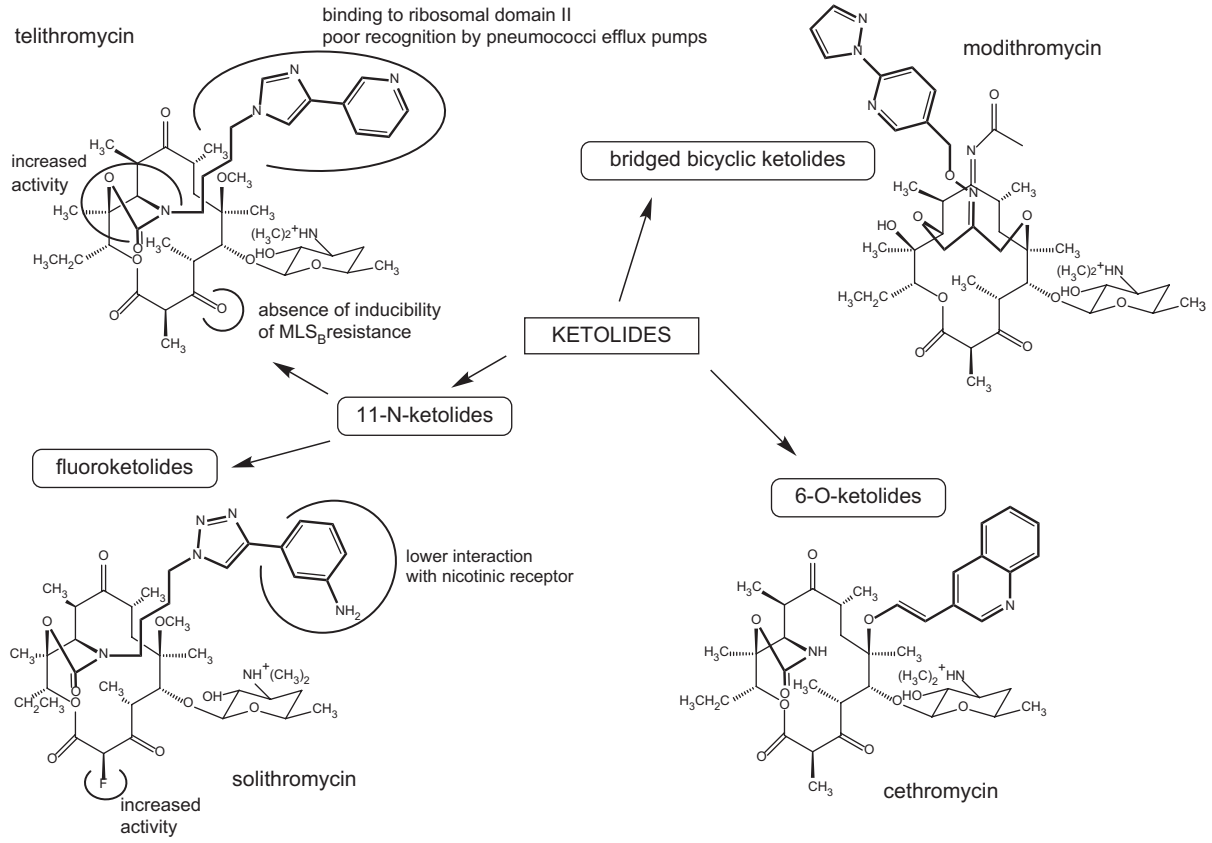

Figure 2. Chemical structure of ketolides in development as compared to telithromycin. Major changes are highlighted together with their main consequences for activity or pharmacokinetics. The structure of EDP-322 having not yet been released, modithromycin is presented as an exemplative typical bridged bicyclic ketolide.

of toxicity issues (81). More frequent reasons for withdrawal include tendinitis (pefloxacin), rash (sparfloxacin, clinafloxacin), QTc prolongation (grepafloxacin), dysglycemia (gatifloxacin, clinafloxacin), hemolysis (temafloxacin), and hepatotoxicity (trovafloxacin) (77,79,81). Resistance to fluoroquinolones is primarily caused by target mutations, which can accumulate and lead to high-level resistance. First-step mutations occur in general in the primary target enzyme (thus more often in GyrA subunit of DNA gyrase in Gram-negative bacteria; ParC subunit of topoisomerase IV in Gram-positive bacteria) (77). Yet, this may vary depending also on the bacterial species, the reverse being notably observed in *S. pneumoniae* (77,82). Active efflux is contributing to decreased susceptibility as well. Gram-positive bacteria do express narrow-spectrum pumps extruding only fluoroquinolones. NorA was historically described as the fluoroquinolone transporter in *S. aureus* (83), but more recent studies suggest a potential role of other efflux pumps in clinical isolates, like NorB, NorC, MdeA (84) or the plasmid-encoded QacA and QacB (85). In *S. pneumoniae*, PmrA was the first described transporter (86), but the heterodimer PatA/PatB is now considered as the main efflux system playing a role in resistance of clinical isolates (87). Of note, there are huge differences in the recognition of different fluoroquinolones by these pumps, norfloxacin and ciprofloxacin being more affected than moxifloxacin, for example (88,89), due to their more hydrophilic character and to the absence of a bulky substituent in position 7. In Gram-negative bacteria, fluoroquinolones are virtually universal substrates of many broad-spectrum transporters (90). By reducing intrabacterial concentration of antibiotics, efflux can contribute to select target mutations and therefore participate in increasing levels of resistance (91). More anecdotal resistance mechanisms include the plasmid-mediated production of the protein Qnr that impairs the binding of fluoroquinolones to DNA (92), or the N-acetylation of fluoroquinolones harboring a piperidine substituent in position 7 (norfloxacin and ciprofloxacin) by an AAC(6')-Ib-cr enzyme originally inactivating aminoglycosides (93). As recently reviewed *in extenso* (94,95), epidemiological surveys performed over the globe demonstrate increasing rates of fluoroquinolone resistance, but huge discrepancies among countries, with the highest figures being observed in the Asia–Pacific region and lower ones in Europe and North America. Considering resistance to ciprofloxacin in Gram-negative species, it can reach more than 20% in uropathogens or bacteria causing intra-abdominal infections. Worryingly enough, much higher values (>70%) are reported in enterobacteriaceae displaying other mechanisms of resistance (including production of extended-spectrum beta-lactamases (96)) or associated with complicated infections. Among enteropathogens, *Campylobacter* species show the highest resistance rate (80% in some reports), but *Salmonella* and *Shigella* often harbor plasmid-mediated resistance and started to spread in the Middle East. More than half of *Escherichia coli* causing traveler's diarrhea are fluoroquinolone-resistant in Asia or Africa. In anaerobes, resistance rates are elevated in some countries (~50%); selection may have occurred after using early-generation fluoroquinolones displaying poor antianaerobic activity. Among respiratory tract pathogens, *Haemophilus influenzae* and *Moraxella catarrhalis* remain susceptible while resistance rates in *Streptococcus pneumoniae* are so far usually low (<4%). Again, at-risk situations include elderly patients, nursing homes, or hospitals. In spite of

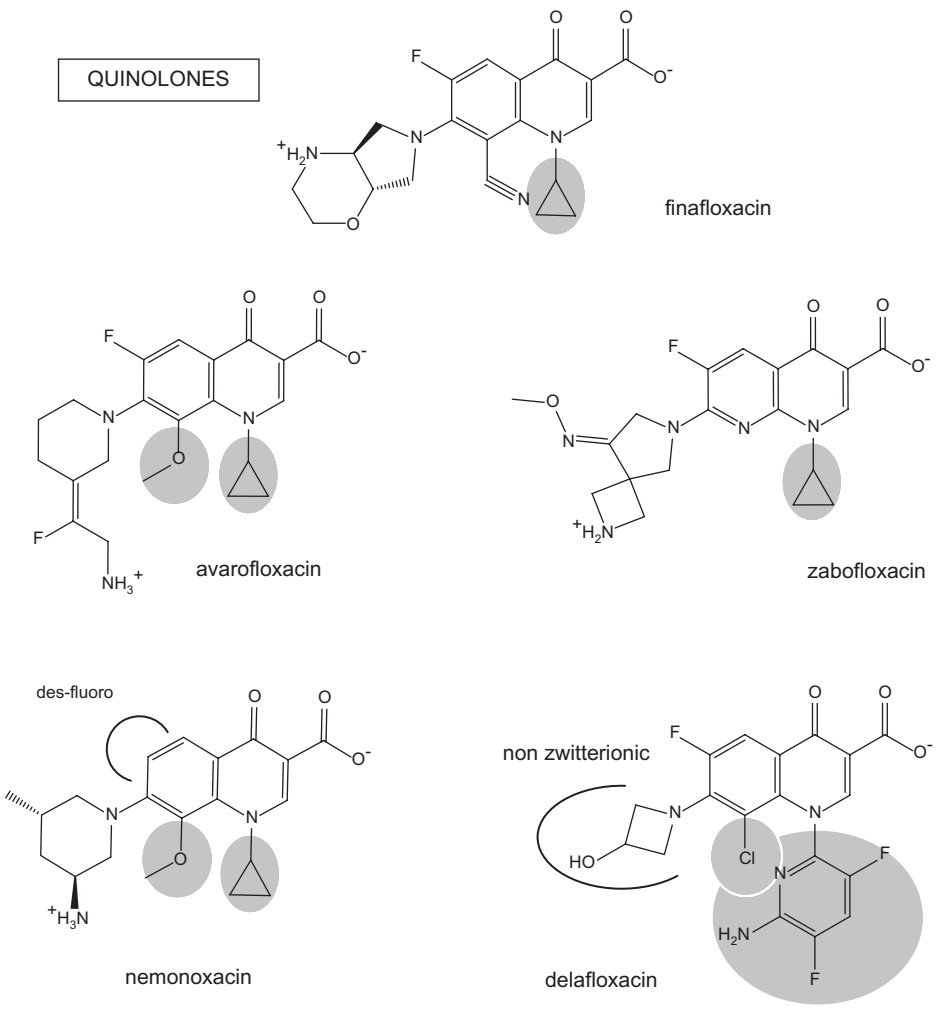

Figure 3. Chemical structure of new fluoroquinolones in clinical development. The substituents in position 1 and 8 known to confer high intrinsic activity are on a gray background. Other specific features are highlighted by black arcs.

fluoroquinolone contra-indication in pediatrics, resistance has been detected in pneumococci isolated from children, possibly due to transmission from adults. In Gram-negative pathogens causing health care-associated pneumonia, resistance rates vary enormously among countries and regions, making local surveillance data indispensable. In bacteria causing skin infections, fluoroquinolone resistance is so common among MRSA that current molecules can no more be considered as valuable therapeutic options. MSSA (methicillin-susceptible *S. aureus*) remain more susceptible, as well as *Streptococcus pyogenes* (with, however, some local spots of higher resistance, like in Belgium (97)). Among pathogens causing sexually transmitted diseases, high variations in resistance rates are observed. The more alarming reports concern *Neisseria gonorrhoeae*, with values ranging from 10% in the US to 60% in Europe and more than 90% in Asia.

In this context, research of new molecules over the last years has focused on the identification of molecules displaying high intrinsic activity including against strains resistant to current fluoroquinolones. This goal was achieved by in-depth structure–activity relationship studies in order to identify the substituents that allow a dual targeting of both topoisomerase IV and DNA-gyrase together with a high binding affinity to these enzymes.

Among the numerous quinolones under study at the present time, five new molecules are in clinical development (Figure 3). They all show increased intrinsic activity, including against strains resistant to current fluoroquinolones, due to an improved interaction with their target enzymes.

Finafloxacin (BAY35-3377; Bayer HealthCare, Wuppertal, Germany; now developed by MerLion Pharmaceuticals GmbH; Singapore and Berlin, Germany) is an 8-cyano-fluoroquinolone. It has the particularity of showing increased bacterial uptake, and therefore enhanced activity, at acidic pH (98–100), a condition which usually reduces the potency of this class of drugs. This constitutes an advantage for the treatment of infections localized in an acidic environment like the urinary and genital tracts, the gastric mucosa, the airways of patients suffering from chronic inflammatory diseases, or abscesses (99) as well as against intracellular infections with phagolysosomal bacteria like *S. aureus* (98). Finafloxacin MICs against ciprofloxacin-susceptible or resistant Gram-negative bacteria are similar to those of ciprofloxacin at neutral pH but 3–5 dilutions lower at pH 5.2 (99–102). It is, however, less active than ciprofloxacin on *Pseudomonas aeruginosa* or other ESKAPE pathogens like *Klebsiella* or *Enterobacter* spp. (101). In contrast to ciprofloxacin, finafloxacin is not a substrate for the fluoroquinolone efflux system by QepA1 of *Escherichia coli* (possibly related to its lower hydrophilicity) and is not affected the AAC(6')-Ib-cr acetylase, as it does not display the piperazine ring substrate for this enzyme in position 7 (100). In phase I studies by oral route, finafloxacin C_{max} was close to 11 mg/L for an 800 mg dose and

an AUC of 28 mg.h/L (Table III). C_{max} increased linearly with the dose, but AUC normalized to the dose increased of about 50% for doses $\geq$400 mg, because elimination was slowed down ($t_{1/2}$ of approximately 5 h for doses lower than 400 mg and 10 h for higher doses). This deviation from linearity is, however, thought to result from inaccurate detection of low concentrations (103). Considering as pharmacodynamic criterion of efficacy an AUC/MIC >125 h^{-1} for infections caused by Gram-negative bacteria (104), a pharmacodynamic breakpoint of 0.25 mg/L could be proposed for this dose. Yet, the drug can reach much higher concentrations in the urine than in serum (103), which may insure its efficacy even for less susceptible bacteria, especially if taking into account the acidic pH of this fluid. The accumulation of the drug within eukaryotic cells (about 5-fold) explains activity on intracellular organisms like *S. aureus*, *L. pneumophila*, or *L. monocytogenes*, with a relative potency and a maximal efficacy similar to those of ciprofloxacin (98). Intracellular potency is, however, improved when cells are incubated at acidic pH, because this condition increases the accumulation of the drug within eukaryotic cells as well. The US Food and Drug Administration has designated finafloxacin for oral and intravenous use as a Qualified Infectious Disease Product and for Fast Track development for the treatment of complicated urinary tract infections (cUTI) including pyelonephritis, complicated intra-abdominal infections (cIAI), and acute bacterial skin and skin structure infections (ABSSSI). It is currently in phase II of clinical development (Table IV). Moreover, the drug has also completed two phase III trials for the treatment of ear infections using topical application, in partnership with Alcon Pharmaceuticals Ltd (Forth Worth, TX, USA).

Avarofloxacin (JNJ-Q2; Janssen Pharmaceutica, subdivision of Johnson & Johnson, licensed to Furiex Pharmaceuticals, Morrisville, NC, USA, in 2011) harbors a cyclopropyl in position 1, a methoxy in position 8, and a bulky, 6-membered aminated substituent in position 7, itself substituted by a fluorine. Avarofloxacin proves more active than moxifloxacin against Gram-positive pathogens, including MRSA or *S. pneumoniae* resistant to fluoroquinolones (Table II). It is also slightly (1–2 dilutions) more active than moxifloxacin against other respiratory pathogens like *H. influenzae* or *M. catarrhalis* (105) and than ciprofloxacin against *N. gonorrhoeae*, against which it also keeps activity on ciprofloxacin-resistant strains (106). *In vitro*, animal and human data assessing cardiovascular safety disclosed a profile comparable to that of moxifloxacin (107). Considering that a free AUC/MIC $= 14$ h^{-1} generates a static effect in animal models of skin infections by *S. aureus*, PK/PD simulations showed a target attainment rate of 0.966 for MIC ≤ 0.5 mg/L if using the drug at an oral dose of 250 mg or an intravenous dose of 150 mg twice daily (108).

This dosage was therefore selected in clinical trials. Pharmacokinetic data from phase I (Table III) reported a C_{max} of approx. 2 mg/L, and AUC of 28 mg.h/L and a half-life of approximately 14 h for an oral dose of 250 mg, with ELF/plasma and alveolar macrophages ratios ranging, respectively, between 17 and 64, and 74 and 157 (109). A first published report of a phase II study showed comparable cure rates for avarofloxacin (150 mg intravenously twice daily followed by 250 mg orally twice daily) and moxifloxacin (400 mg once daily, intravenously or orally) for the treatment of community-acquired infection (110). Yet, the number of patients was too small (16 in each arm) to perform in-depth statistical analyses. Avarofloxacin received a Qualification as Infectious Disease Product and Fast Track designation from the US FDA in February 2013 and is ready to start phase III trials for the treatment of acute bacterial skin and skin-structure infections and community-acquired pneumonia.

Zabofloxacin (DW-224a; Dong Wha Pharmaceuticals Industry, Ltd; Anyang City, Korea) is constructed on a naphthyridone nucleus. It presents a cyclopropyl substituent in position 1 and a bulky, pyrrolidine-based substituent in position 7, which directs its spectrum towards Gram-positive bacteria. It targets both DNA gyrase and topoisomerase IV in *S. pneumoniae*, which reduces the risk of selection of resistance (111). It is in general 2–16 times more potent than moxifloxacin on Gram-positive bacteria but 2–4 times less potent than ciprofloxacin against Gram-negative bacteria (112). It is also more potent than ciprofloxacin against *N. gonorrhoeae* or *C. trachomatis*, suggesting it could be an appealing alternative to ciprofloxacin against macrolide-resistant strains (113). A phase I trial evidenced a C_{max} of approximately 2 mg/L and a 24-h AUC of approximately 11 mg.h/L after a single oral dose of 400 mg (Table III) (114). A phase II trial comparing zabofloxacin (400 mg QD for 3 or 5 days) to moxifloxacin (400 mg QD for 7 days) for the treatment of mild to moderate community-acquired pneumonia concluded the clinical and microbiological cure rates were similar, with no sign of side effects (115). A second phase II trial has compared it to levofloxacin in the same indication (Table IV). Zabofloxacin is claimed to be in late stage of phase III development for respiratory tract infections by Gram-positive resistant bacteria, but no additional information has been made available.

Nemonoxacin (TG-873870; TaiGen Biotechnology Co., Ltd., Taiwan) is a desfluoroquinolone harboring a methoxy group in position 8 and a 6-membered aminated substituent in position 6. It is globally 2–8-fold more potent than moxifloxacin against most Gram-positive cocci but 4-fold less potent than ciprofloxacin against Gram-negative bacilli (116). Additionally, it also shows useful activity on *Chlamydia* spp. (117) or *Clostridium difficile* (118).

In preclinical studies, nemonoxacin was minimally metabolized (less than 5% metabolites recovered) and did not influence human hepatic CYP3A4 activity; it had minimal effect on cardiac conduction as measured by ECG QTc interval prolongation and a low phototoxic potential (119 and references cited therein). Human pharmacokinetic data for the oral route (Table III) showed a C_{max} around 3.5–5 mg/L and an AUC of approximately 32 mg.h/L for a dose of 500 mg, a low protein binding (16%) but a half-life of 10–15 h (longer upon administration of higher doses). This allows for a once-a-day mode of administration while maintaining free serum levels about the MIC of target pathogens (119,120). AUC was decreased of about 17% by food intake. The most common adverse effect observed in phase I was headache (120). *In vitro* pharmacodynamic studies suggest that a 3-log kill could be achieved against *S. pneumoniae* for free AUC/MIC ratio >47.5 h^{-1} (121). This is consistent with the globally accepted concept that the probability for therapeutic success with quinolones is free AUC/MIC ratio >25–40 h^{-1} for Gram-positive bacteria (122). A pharmacodynamic breakpoint of ~0.5 mg/L could be proposed on these bases, which is well above the MIC distribution of pneumococci (Table II) and can partly cover MRSA. The drug completed two phase II clinical trials with the oral formulation for community-acquired pneumonia and diabetic foot infection, and one phase II clinical trial with the intravenous formulation for community-acquired pneumonia, as well as one phase III trial for the treatment of community-acquired pneumonia by oral route. The results of one of these trials were published (123) and showed that nemonoxacin (750 mg or 500 mg) orally for 7 days was as effective as levofloxacin (500 mg), with 1) clinical success rates close to 90%, 2) bacterial eradication of 90% in the 750 mg dose and the levofloxacin groups versus 85% in the 500 mg dose group, and 3) good tolerability. The US

FDA granted nemonoxacin Qualified Infectious Disease Product and Fast Track designations for community-acquired bacterial pneumonia (CAP) and acute bacterial skin and skin structure infections (ABSSSI) in December 2013.

Delafloxacin (WQ-3034, discovered by Wakunaga Pharmaceutical Co., Ltd., Osaka & Hiroshima, Japan; further developed as ABT-492, Abbott Park, IL, USA, and then as RX-3341 by Rib-X Pharmaceuticals Inc., New Haven, CT, USA; now Melinta Therapeutics, New Haven, CT) has the unique property of being an anionic fluoroquinolone, as it lacks a positively charged substituent in position 7. This chemical feature rationalizes why it accumulates much more in both bacteria and eukaryotic cells at acidic pH (124). Delafloxacin shows very low MICs against Gram-positive pathogens, with values typically 4 dilutions lower than those of moxifloxacin, even against strains showing elevated MIC to the reference drug (124). At acidic pH, the difference in potency between the two antibiotics can reach 7 dilutions (124). The high potency of delafloxacin is thought to result from the specific shape, size, and polarity of the molecule as compared to conventional fluoroquinolones (125). Although designed as an anti-Gram-positive drug, it is also at least as potent as ciprofloxacin against Gram-negative bacteria, including *P. aeruginosa* (Table II). Selection of resistance in *S. aureus* is infrequent (10^{-9} to 10^{-11}), and concentrations preventing the selection of mutations (MPC (126)) range from 1 to 4 times the initial MIC, with values 8- to 32-fold lower than for other quinolones (127). Delafloxacin also proved active in *in vitro* models of biofilm or intracellular infection by *S. aureus* (124,128), despite the fact it mainly localizes in the cytoplasmic compartment of cells (124). This may be due to the high diffusibility of fluoroquinolones, which may help them freely to cross biological membranes within the cells to gain access to the infected compartment. Efficacy was further documented in animal models of granuloma pouch by Gram-negative bacteria and thigh infection or renal abscess by *S. aureus* (129–131).

In phase I trials (Table III), delafloxacin showed a C_{max} of 10 and 16 mg/L and an AUC of 24 and 40 mg.h/L after IV administration of 300 and 450 mg, respectively, with a free fraction of 84% and a half-life of 8–12 h (132,133).

Similar values (slightly lower C_{max} (7 mg/L)) were observed in phase II patients treated for acute bacterial skin and skin structure infections by a daily dose of 300 mg intravenous and BID (134). Elimination is mainly renal, but metabolites have been detected, among which a glucuronoconjugate (135). The dose should be reduced from 300 to 200 mg IV in case of renal insufficiency (136). Based on a pharmacodynamic target of fAUC/MIC = 25–40 h^{-1} for Gram-positive infections (122), a pharmacodynamic breakpoint of 0.5 mg/L could be proposed, which covers most of the strains, including fluoroquinolone-resistant ones. This is in accordance with PK/PD animal data (137) and Monte Carlo simulations, which concluded to a $>90\%$ target attainment rate for MICs ≤ 0.5 mg/L upon administration of 300–450 mg BID (133), and rationalizes the doses used in phase III trials (Table IV). Safety data available so far did not reveal any specific adverse events (132,138), including on the cardiac function (no prolongation of QTc interval (139)). Published data from phase II clinical trials demonstrated equal efficacy in the treatment of acute bacterial infection of skin and skin structure infection (ABSSSI) for delafloxacin 300 mg IV BID as compared to linezolid or vancomycin but better efficacy when considering as end-point a reduction $>20\%$ or $>30\%$ in lesion size after 48–72 hours (138,140). The US FDA has granted delafloxacin the status of a Qualified Infectious Disease Product for the indications of acute bacterial skin and skin structure infections (ABSSSI) and community-acquired bacterial pneumonia (CABP) in October 2012. It is currently in phase III of clinical development for acute bacterial infection of skin and skin structure infection and uncomplicated gonorrhea based on its excellent *in vitro* activity against *N. gonorrhoeae*, including ciprofloxacin-resistant strains (141).

Conclusion

At the end of this survey, one can see that the molecules in the last stages of development mainly address the question of resistance in Gram-positive pathogens, among which MRSA and VRE belong to the so-called ESKAPE pathogens. Oritavancin consistently shows low MIC on VRE, multiresistant pneumococci, MRSA, but also VRSA and, to some extent, VISA. Solithromycin and new quinolones (except finafloxacin) bring in general an impressive response to resistance to earlier-generation molecules in staphylococci and pneumococci. Some variations do, however, exist among fluoroquinolones, with avarofloxacin and delafloxacin being the more potent on MRSA. Delafloxacin and finafloxacin display a clear advantage for infections located in acidic territories caused, respectively, by Gram-positive and Gram-negative bacteria. While being the only molecule rather directed towards Gram-negative bacteria, finafloxacin does not offer any advantage over ciprofloxacin on ESKAPE pathogens.

Oritavancin can be considered as a member of a totally new antibiotic class, since its mode of action is clearly different from that of conventional glycopeptides. It could usefully complement the only marketed molecule in this class, telavancin, by a somewhat higher activity on VRSA and VRE and, most conspicuously, by its original mode of administration, which clearly offers a series of advantages in terms of ease of use and reduction of hospitalization duration.

Ketolides and new quinolones essentially offer improved intrinsic activity as compared to earlier molecules, which was reached by optimizing their binding to the pharmacological targets. Hopefully enough, the dose of all of them has being rationally established based on PK/PD concepts, which should help limiting the risk of selection of resistance if used appropriately. Yet, we clearly need much more data related to their clinical efficacy on multidrug-resistant pathogens and their safety profile. For registration, health authorities demand at this stage the demonstration of an equivalence to standard treatment, which, by definition, prevents the investigators from enrolling patients infected by bacteria resistant to the comparator. These resistant strains are indeed actually the main targets for the new drugs. The scientific community is therefore pushing for the inclusion of non-comparative trials directed to the evaluation of new antibiotics against these specific populations or of superiority trials in the development plan of new antibiotics (142). With respect to safety issues, experience with previously marketed molecules has shown that severe adverse reactions were too rare to be detected during clinical development. Post-marketing surveillance is therefore essential. Moreover, one can argue that reasonable use, meaning limited to infections sufficiently severe really to require antibiotic treatment, should contribute to contain this risk. This would go through the establishment of rational and regularly updated guidelines for the treatment of bacterial infections in order to preserve the interest of these new molecules we are looking forward to seeing on the market.

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