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Ketolides: pharmacological profile and rational positioning in the treatment of respiratory tract infections

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Ketolides differ from macrolides by removal of the 3-*O*-cladinose (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. These modifications allow for anchoring at two distinct binding sites in the 23S rRNA (increasing activity against erythromycin-susceptible strains and maintaining activity towards *Streptococcus pneumoniae* resistant to erythromycin A by ribosomal methylation), and make ketolides less prone to induce methylase expression and less susceptible to efflux in *S. pneumoniae*. Combined with an advantageous pharmacokinetic profile (good oral bioavailability and penetration in the respiratory tract tissues and fluids; prolonged half-life allowing for once-a-day administration), these antimicrobial properties make ketolides an attractive alternative for the treatment of severe respiratory tract infections such as pneumonia in areas with significant resistance to conventional macrolides. For telithromycin (the only registered ketolide so far), pharmacodynamic considerations suggest optimal efficacy for isolates with minimum inhibitory concentration values ≤ 0.25 mg/l (pharmacodynamic/pharmacokinetic breakpoint), calling for continuous and careful surveys of bacterial susceptibility. Postmarketing surveillance studies have evidenced rare, but severe, side effects (hepatotoxicity, respiratory failure in patients with myasthenia gravis, visual disturbance and QTc prolongation in combination with other drugs). On these bases, telithromycin indications have been recently restricted by the US FDA to community-acquired pneumonia, and caution in patients at risk has been advocated by the European authorities. Should these side effects be class related, they may hinder the development of other ketolides such as cethromycin (in Phase III, but on hold in the US) or EDP-420 (Phase II).

Keywords: cethromycin, EDP-420, *Streptococcus pneumoniae*, telithromycin

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1. From macrolides to ketolides

Ketolides in present clinical use or in development are semisynthetic derivatives of erythromycin A with activity against clinically important erythromycin-resistant organisms.

The structural characteristics responsible for this property are: i) removal of the cladinose normally present at position 3 and its replacement by a keto-group (hence the name ketolides); ii) incorporation of an 11,12- or 6,11-cyclic moiety; and iii) addition of a heteroaryl-alkyl side chain attached to the macrocyclic ring by a suitable linker.

Macrolides lacking cladinose were actually identified almost at the same time as erythromycin A (or even before), as natural products such as picromycin or narbomycin. These molecules, however, had a weak antibacterial potency and a poor oral absorption and were not further developed until it was demonstrated in the late 1970s that they do not induce resistance in *Staphylococcus aureus*, while at the same time remaining active against strains having developed resistance to erythromycin A and other conventional macrolides [1]. As macrolides, picromycin and narbomycin inhibit protein synthesis by binding to the 50S ribosomal subunit, close to the peptidyl transferase site at the entrance of the ribosomal exit tunnel (**Figure 1**). Thus, both types of molecules interact with nucleotides A2058 and A2059 in the domain V, but the lack of cladinose makes this binding less tight for picromycin or narbomycin. To improve their activity, a systematic pharmaco-chemical development was initiated at Roussel-Uclaf in 1988, but starting from erythromycin A, which was well known and had a better bioavailability than narbomycin. This led to a series of compounds derived from erythromycin A, but lacking the cladinose and presenting an additional, flexible hetero-aryl-alkyl side chain attached via a suitable linker to the macrocyclic ring. This allows the molecules to bind to an additional site on the ribosome (namely in the vicinity of A752 in domain II), and markedly increases their affinity for the ribosomes. As a result, they are more active against erythromycin-susceptible strains, and remain capable of interacting with ribosomes from erythromycin-resistant organisms in which the A2058 nucleotide is methylated (through the activity of the *erm* gene; **Figure 1**; see for reviews [2,3]). The lack of cladinose also makes ketolides unable to act as inducers in strains presenting the inducible form of this resistance. In addition, it may prevent recognition of the molecule by the Mef efflux pumps, at least in pneumococci [4]. Ketolides remain, however, susceptible to resistance by efflux in *Streptococcus pyogenes* [5].

This discovery stimulated active research in order to design other molecules with similar or improved properties. Many of them have now been obtained, allowing us to refine our view of structure–activity relationships within this family (**Figure 2**), and leading to a subclassification of the ketolides (see [4,6,7] for reviews and [8,9] for an original description of the chemistry of ketolides compared with that of macrolides). So far, three main families have been described giving rise to compounds with clinical use or demonstrated potential, in which the aryl-alkyl chain has been attached in position 11, 6 or to both positions. In the later case, the keto group in position 9 is also replaced by an iminoether (see **Figure 2**). In the 11-*N*-ketolides group, the hetero-aryl-alkyl side chain is attached to the macrocycle through the N atom of a 11,12-cyclic carbamate [10,11], with telithromycin (HMR-3647) [12], the first ketolide in clinical use, as a typical example. In the 6-*O*-ketolides group, the hetero-aryl-alkyl group is attached to the macrocycle through the O atom in position 6 of the lactone ring [13-18]. Cethromycin (ABT-773) is a typical example of this family [19] and is presently in Phase III of clinical trials (but its development seems now on hold [20]). In the so-called bridged bicyclic ketolides, the heteroaryl side chain is attached to an oxime moiety centered on a three-carbon bridge linking the 6- and 11-hydroxyl groups of the macrocycle (hence the name bridged bicyclic). EDP-420 (also known as EP-013420 or S-013420 [21]) is the first example of these compounds being brought forward and is in Phase II of clinical development.

Acid stability (essential to obtain a high and reproducible oral bioavailability) of the above-mentioned compounds is ensured by the lack of cladinose on the one side [9], as well as by methylation of the 6-*O* position for telithromycin (as in clarithromycin), and by the linker used to attach the heteroaryl-alkyl side chain for cethromycin and EDP-420. In EDP-420, the 9-keto function of erythromycin has also been replaced by an acetylimino function. These modifications indeed prevent the ketalisation reaction occurring in erythromycin A between the keto group in position 9 and the hydroxyle group in position 6 or 3 [22].

Many other investigational compounds belonging to other subfamilies (such as 2-fluoroketolides [23-25], C-9 iminoether ketolides in which the carbamate has been replaced by a carbonate [26-28], C-12 or C-13 modified ketolides [29,30], 15-membered ring ketolides [31], and tricyclic or tetracyclic ketolides [32]) have also been described, but the corresponding derivatives seem still far from clinical development.

2. *In vitro* antibacterial activity and resistance

Table 1 compares the *in vitro* activity of the three ketolides in clinical use or development to that of erythromycin A against bacteria responsible for respiratory tract infections, including intracellular pathogens. Erythromycin-susceptible strains, telithromycin and cethromycin, and EDP-420 to some extent, show much lower minimum inhibitory concentration (MIC) values, as anticipated from their design. Most interestingly also, their MIC values are only modestly increased (one to three dilutions) against streptococci with the efflux or ribosomal methylation mechanism of resistance. Constitutive ribosomal mutations, however, make both telithromycin and cethromycin inactive towards *S. aureus*, and, for telithromycin, towards *S. pyogenes* [33,34]. As for erythromycin A, ketolides show low MIC values towards atypical and intracellular pathogens involved in pneumonia [35] and respiratory Gram-negative bacteria [36]. Notably, they prove as active as azithromycin and more active than other macrolides against intracellular *Legionella* both in *in vitro* and *in vivo* models [37-39]. However, like erythromycin A and most other conventional macrolides, ketolides remain poorly active against *Haemophilus influenzae*. This is actually no surprise as their design was not specifically oriented towards an improvement of activity against Gram-negative organisms.

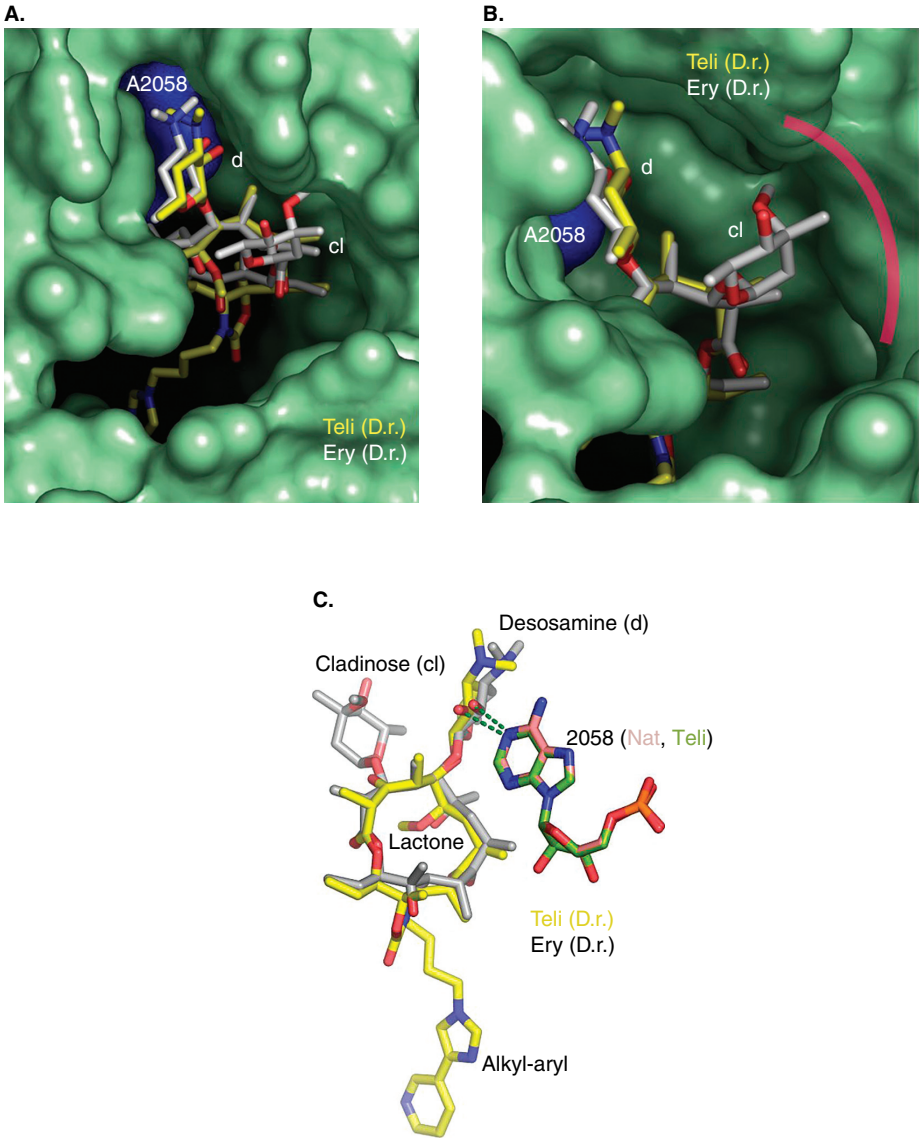

Figure 1. Comparison of the mode of interaction of erythromycin A and telithromycin with 23S rRNA (see also [3,148]). **A.** View onto the ribosomal exit tunnel entrance of the 50S model from *Deinococcus radiodurans* (D.r, D50S), 23S rRNA is displayed as mint surface (Ade2058 is marked in blue, *E. coli* numbering used for figures). Macrolides like erythromycin A (Ery, grey) and ketolides like telithromycin (Teli, yellow) inhibit translation by blocking the ribosomal exit tunnel [3,149] and thus prevent the nascent peptide chain to move forward, which leads to translation arrest in most cases. **B.** Zoom and slightly different orientation of **A.** Methylation or mutation A- > G of Ade2058 has as consequence that the hydrogen bond of the desosamine-moiety (d) of the macrolides/ketolides to 2058 (see also **C**) is not possible and that the antibiotic needs to be shifted away from A2058. The cladinose moiety (cl), close to the tunnel wall (pink line) restricts possible positionings of the macrolides (Ery, grey) for alternative binding to ribosomes with mutated or methylated 2058. Ketolides (Teli, yellow) lacking the cladinose have much more room for an alternative positioning which, together with the additional, stabilizing binding of their alkyl-aryl side chain, can overcome A2058 methylation/mutations in many bacteria. **C.** Macrolides and ketolides bind in similar mode to the ribosome. The lactone ring overlaps with high agreement and the hydrogen bonds (green dotted) between Ade2058 (of 23S; Nat, native, position in the absence of antibiotic; teli, position in the presence of telithromycin) and the desosamine-moieties differ only slightly for telithromycin (yellow, 2058 in green) and erythromycin A (grey, 2058 in pink) in D50S.

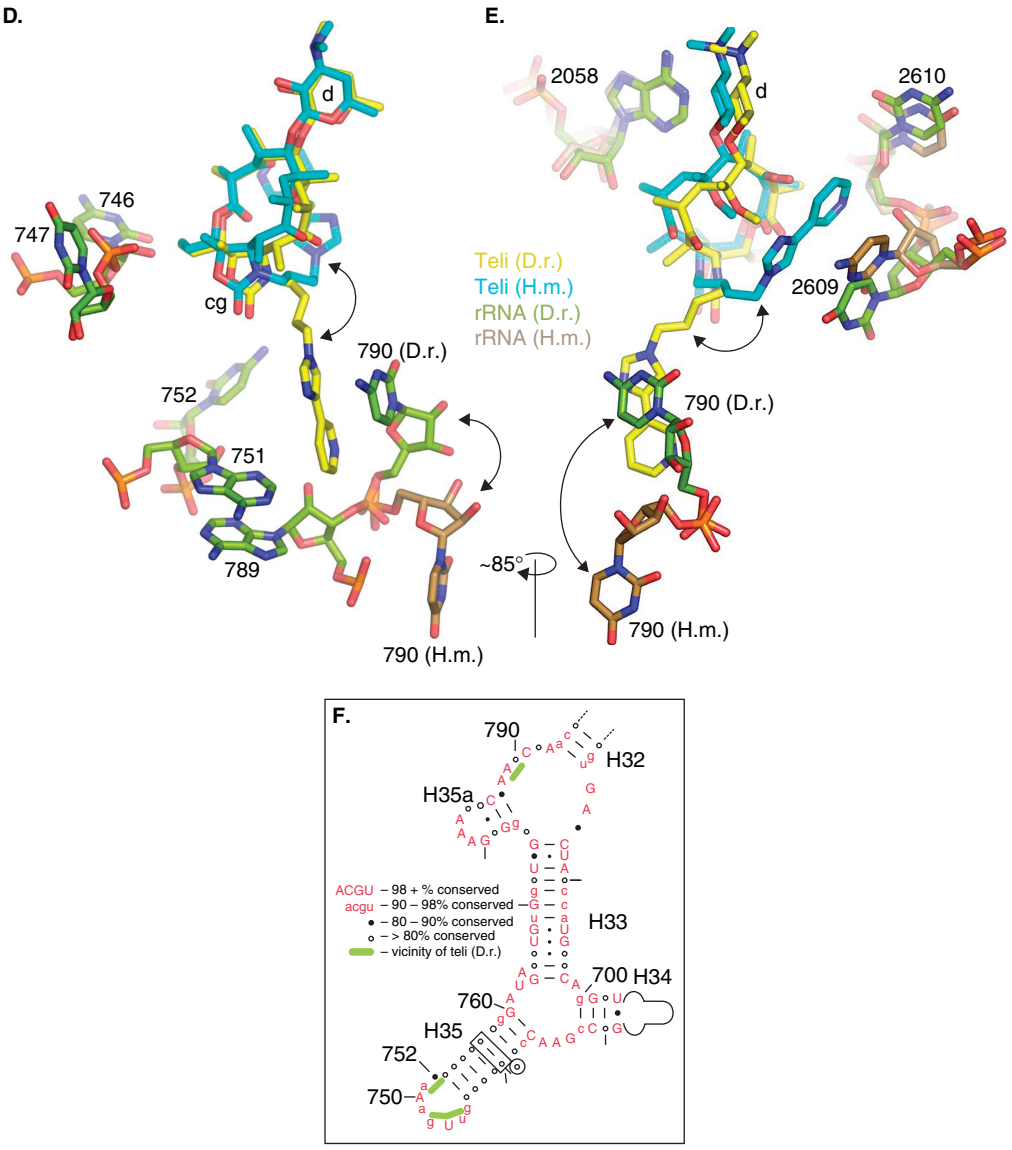

Figure 1. Comparison of the mode of interaction of erythromycin A and telithromycin with 23S rRNA (see also [3,148]) (continued). **D.** Comparison of position and conformation of telithromycin bound to D50S (yellow) and to a G2058A mutated *Haloarcular marismortui* 50S subunit (H.m., H50S, in cyan) [150], show the lactone ring position in good agreement whereas the alkyl-aryl side chain adopts dramatically different orientations (arrowed). In D50S the alkyl-aryl side chain penetrates deeper into the tunnel, contacting nucleotides of dom II of 23S, binding mainly through stacking to U790. For the A2058G mutated H50S the orientation of the alkyl-aryl side chain has been found folded back across the lactone ring, interacting to nucleotides of dom VI of 23S rRNA. Dom II of 23S rRNA is very similar for D50S and H50S. Nevertheless there is a dramatic difference: C790 not only has a different 'sequence' but also shows to be about 180 deg rotated away compared to D50S (arrowed) which offers less options for interaction for the side chain with dom II in H50S. **E.** About 85 deg rotated view of **D.** For the sake of clarity only the main binding nucleotides are shown. In H50S-A2058E the alkyl-aryl-side chain (cyan) is stacking to 2609 of dom VI (brown). This way there is no remarkable additional contact to dom II compared to macrolides. Covering a similar area as the cladinose-moiety of macrolides, this positioning of the side chain in H50S leads to a similar restriction of the free room for the adoption of an alternative orientation of the antibiotic in case of a 2058 mutation or methylation. Note: Telithromycin does not bind to native H50S (G2058) [150]. The complexes of D50S and H50S with telithromycin demonstrate the highly mobility of its alkyl-aryl side chain, which is an advantage for overcoming macrolide resistance and structural variations between bacteria. **F.** Secondary structure of H33-H35 of the *E. coli* 23S rRNA, with the conservation of this region based on 436 bacterial sequences, nucleotides close to telithromycin (D.r.) are marked green [151]. In general the single stranded rRNA of the dom II binding region is relatively well conserved (> 80% or better). Nevertheless, flexible extensions of ketolides that reach the dom II region are supposed to deal better with small variations in sequence and structure of this area of the 23S-rRNA.

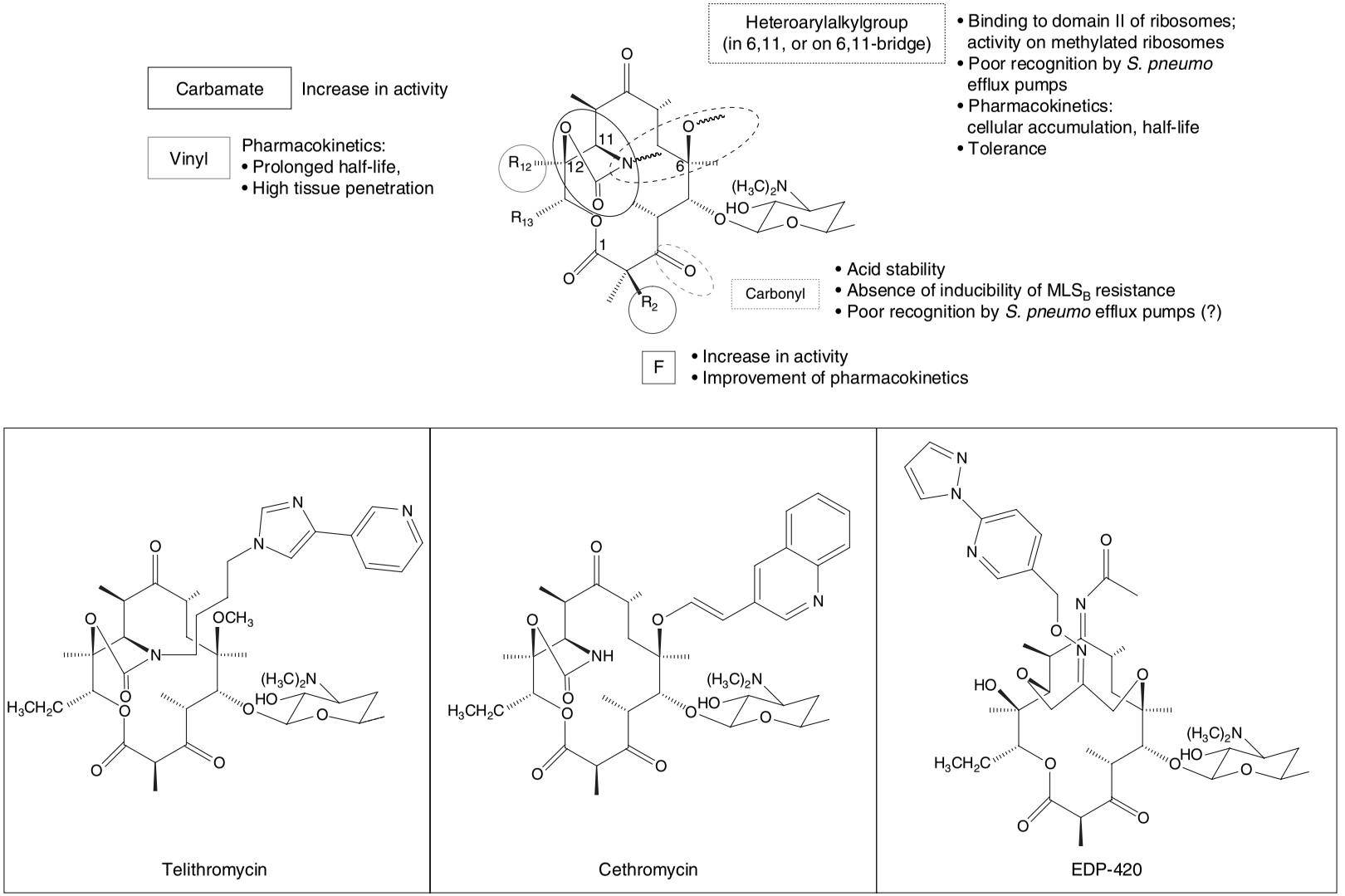

Figure 2. Structure–activity relationships for ketolides (based on [4,7,9,29,152]) and chemical structure of ketolides on the market or in clinical stage of development.

Table 1. *In vitro* activity of ketolides (telithromycin, cethromycin, EDP-420) compared with erythromycin A (or clarithromycin).

	Phenotype	Drug	MIC_{50} (mg/l)	MIC_{90} (mg/l)	MIC range (mg/l)	Nb strains	Ref.
Staphylococcus aureus	Macrolide susceptible	Erythromycin A	0.5	1	0.12 – 1	60	[34]
		Telithromycin	0.03	0.06	0.008 – 0.5	60	[34]
		Cethromycin	0.008	0.03	0.008 – 0.25	60	[34]
	All (both susceptible and resistant)	Erythromycin A	> 32	> 32	≤ 0.03 – > 32	100	[138]
		Telithromycin	0.13	> 32	≤ 0.03 – > 32	100	[138]
		EDP-420	0.13	> 32	≤ 0.03 – > 32	100	[138]
	Inducible ribosomal methylation	Erythromycin A	> 32	> 32	0.5 – > 32	47	[34]
		Telithromycin	0.12	0.5	0.03 – 0.5	47	[34]
		Cethromycin	0.03	0.06	0.004 – 0.12	47	[34]
	Constitutive ribosomal methylation	Erythromycin A	> 32	> 32	16 – > 312	60	[34]
		Telithromycin	> 32	> 32	0.06 – > 32	60	[34]
		Cethromycin	> 32	> 32	≤ 0.008 – 32	60	[34]
Streptococcus pneumoniae	All (both susceptible and resistant)	Erythromycin A	0.06	32	≤ 0.015 – > 64	312	[139]
		Telithromycin	≤ 0.015	0.25	≤ 0.015 – > 4	312	[139]
		Cethromycin	0.008	0.06	≤ 0.004 – > 16	312	[139]
		EDP-420	0.03	0.25	≤ 0.015 – 2	200	[138]
	Efflux	Erythromycin A	4	8	2 – 16	50	[140]
		Telithromycin	0.12	0.25	0.008 – 1	50	[140]
		Cethromycin	0.06	0.12	≤ 0.004 – 0.25	50	[140]
		EDP-420	0.12	0.5	≤ 0.015 – 0.5	40	[138]
	Ribosomal methylation	Erythromycin A	> 128	> 128	2 – > 128	45	[140]
		Telithromycin	0.008	0.5	0.008 – 8	45	[140]
		Cethromycin	0.03	0.25	0.008 – 2	45	[140]
		EDP-420	0.06	0.5	≤ 0.015 – 2	20	[138]
	Efflux plus ribosomal methylation	Erythromycin A	> 128	> 128	0.5 – > 128	39	[34]
		Telithromycin	0.12	0.25	≤ 0.002 – 0.5	39	[34]
		Cethromycin	0.06	0.25	≤ 0.002 – 0.5	39	[34]
Streptococcus pyogenes	Susceptible	Erythromycin A	0.06	0.06	0.03 – 0.12	60	[140]
		Telithromycin	0.03	0.03	0.004 – 0.25	60	[140]
		Cethromycin	0.03	0.03	≤ 0.004 – 0.03	60	[140]
		EDP-420	≤ 0.03	≤ 0.03	≤ 0.03 – 0.13	102	[138]
	Efflux	Erythromycin A	8	8	2 – 16	10	[140]
		Telithromycin	0.06	0.25	0.008 – 0.5	10	[140]
		Cethromycin	0.06	0.12	0.008 – 0.25	10	[140]

MIC: Minimum inhibitory concentration; nd: No data provided.

Table 1. *In vitro* activity of ketolides (telithromycin, cethromycin, EDP-420) compared with erythromycin A (or clarithromycin) (continued).

	Phenotype	Drug	MIC_{50} (mg/l)	MIC_{90} (mg/l)	MIC range (mg/l)	Nb strains	Ref.
	Inducible ribosomal methylation	Erythromycin A	16	32	2 – 128	10	[140]
		Telithromycin	0.12	0.5	0.008 – 2	10	[140]
		Cethromycin	0.12	0.25	0.008 – 2	10	[140]
	Constitutive ribosomal mutation	Erythromycin A	> 128	> 128	2 – > 128	35	[141]
		Telithromycin	2	8	0.03 – 8	35	[141]
		Cethromycin	nd	nd	0.01 – 1	8	[33]
Moraxella catarrhalis	Macrolide susceptible	Erythromycin A	0.12	0.25	0.12 – 0.5	428	[140]
		Telithromycin	0.06	0.12	0.015 – 0.25	428	[140]
		Cethromycin	0.06	0.12	0.015 – 0.25	428	[140]
Haemophilus influenzae	Macrolide susceptible	Erythromycin A	4	8	0.03 – 32	213	[140]
		Telithromycin	2	4	0.06 – 8	213	[140]
		Cethromycin	2	4	0.03 – 8	213	[140]
Chlamydia pneumoniae	Macrolide susceptible	Erythromycin A	0.15	0.25	0.015 – 0.25	19	[35]
		Telithromycin	0.0625	0.25	0.031 – 2	19	[35]
		Cethromycin	0.015	0.015	0.008 – 0.015	20	[35]
Legionella pneumophila	Macrolide susceptible	Clarithromycin	≤ 0.004	≤ 0.004	nd	20	[35]
	Macrolide susceptible	Telithromycin	0.03	0.03	nd	20	[35]
		Cethromycin	0.016	0.064	0.004 – 0.125	20	[38]
Mycoplasma pneumoniae	Macrolide susceptible	Erythromycin A	≤ 0.001	≤ 0.004	≤ 0.001 – 0.016	103	[142]
		Telithromycin	0.0005	0.0005	0.0002 – 0.0005	nd	[143]
		Cethromycin	≤ 0.001	≤ 0.001	≤ 0.001 – 0.016	103	[142]
		EDP-420	0.001	0.001	0.0005-0.001	nd	[143]

MIC: Minimum inhibitory concentration; nd: No data provided.

On a positive side, low or lack of significant activity against Gram-negative pathogens may be viewed as an advantage in terms of lesser impact on resistance development in commensal and non-respiratory bacteria [36].

2.1 Resistance to ketolides

Based on Clinical and Laboratory Standards Institute (CLSI) breakpoints (S: ≤ 1 mg/l; I: 2 mg/l; R: ≥ 4 mg/l), most clinical isolates of streptococci collected through surveillance studies can still be classified as telithromycin susceptible. Pharmacokinetic/pharmacodynamic considerations (see next paragraph), however, suggest that the pharmacokinetic/pharmacodynamic breakpoint of telithromycin should be lower (see **Table 2**), so that a non-negligible proportion of isolates should actually be considered as the 'reduced susceptibility' type (see e.g., [40,41]). Examination of a collection of 1640 strains of *Streptococcus pneumoniae*, indeed, shows that the telithromycin MIC distribution is bimodal, with 30% of the isolates displaying higher MIC (0.06 – 0.5 mg/l) than the main population. These correspond essentially to erythromycin-resistant strains (with the *erm* mechanism) [42]; the weaker activity of telithromycin in these strains may result from dimethylation at A2058 nucleotide, as shown in *S. pyogenes* [43].

True ketolide-resistant pneumococcal strains have also begun to emerge, even though they remain anecdotal so far. A recent PROTEKT (Prospective Resistant Organism Tracking and Epidemiology for the Ketolide Telithromycin) study reports indeed 0.1% of the 20750 strains with a telithromycin MIC ≥ 4 mg/l [44]. More local data suggest that this prevalence could be much higher, with heterogeneous telithromycin resistance detected in 13% of macrolide-resistant *S. pneumoniae* in Finland [45], and 15% of pneumococci displaying an MIC ≥ 2 mg/l in Taiwan [46].

The situation is probably more alarming for *S. pyogenes*, with telithromycin resistance reaching 5.8 and 10% of erythromycin-resistant isolates from Greece and Belgium, respectively [47,48]. This resistance to telithromycin has

Table 2. Main pharmacokinetic parameters of telithromycin and cethromycin.

Drug	Dose	Compartment	C_{max} (mg/l)	AUC (mg·h/l)	Half-life (h)	Prot. binding (%)	PD Bkpt (fAUC/MIC > 25) [71]	Ref.
Telithromycin	800 mg po	Serum	1.9 – 2.5	10.4 – 13.4	9.8 – 13.3	70	~ 0.2	[80]
		ELF*	5 – 36	~ 160‡				[144,145]
		Alveolar cells*	22 – 126	~ 4300‡				[144,145]
Cethromycin	300 mg po	Serum	0.5	3.1	4.94	90	~ 0.015	[146]
		ELF*	2.75	24.2				[146]
		Alveolar cells*	55.4	636.2				[146]

*At day 5.

‡Value calculated from pharmacokinetic profile in these compartments [145].

ELF: Epithelial lining fluid; PD Bkpt: Maximal MIC for which a (free AUC/MIC) ratio > 25 can be reached (pharmacodynamic criterium of efficacy); po: By mouth.

been associated with mutations in domains II and V of 23S rRNA as well as in L22 or L4 ribosomal proteins [49-57]. However, resistance by efflux was also demonstrated in clinical isolates and of *S. pyogenes* with MIC values ≥ 0.5 mg/l [5] and considered to account for the intrinsic poor susceptibility of *H. influenzae* [58]. Telithromycin MIC may rise to ≥ 4 mg/l when efflux is combined with ribosomal mutations.

Two other mechanisms of resistance to telithromycin have also been described. The first one consists in the production of 'incomplete' or class 2 ABC transporters (called MsrA in *S. aureus* and MsrD in *S. pneumoniae*), which confers resistance to macrolides and, in some cases, also to streptogramins B, lincosamides or ketolides [59]. These proteins act by reducing the accessibility of the ribosomal target site for the antibiotics, reducing in proportion the driving force for antibiotic import [60]. The second one is related to the production of macrolide phosphorylases, which confers cross-resistance to all macrolides and ketolides [61], and is seen in Gram-negative bacteria.

Other ketolides should in principle be also affected by resistance mechanisms reducing telithromycin activity, but cross-resistance data are lacking so far.

3. Pharmacokinetics and pharmacodynamics

Table 2 shows the main pharmacokinetic parameters of telithromycin and cethromycin, and the corresponding calculated pharmacodynamic breakpoints.

Both drugs are characterized by relatively low serum concentrations, which can be ascribed to their large volume of distribution. As macrolides, these drugs are weak bases due to the presence of the aminated desosamine sugar (see **Figure 2**), which causes their preferential accumulation by proton trapping in the acidic compartments of the cells (see for review [62]). An active mechanism requiring protein kinase A- and tyrosine kinase-dependent phosphorylation was also proposed to occur [63], but the corresponding macrolide carrier was never evidenced. Thus, *in vitro* studies demonstrate that ketolides accumulate to high levels in both phagocytic and non-phagocytic cells [64-66]. Their cellular disposition can, however, be modulated by the activity of multidrug transporters. It has been shown that telithromycin is a substrate for P-glycoprotein in macrophages [67], which could affect its activity towards intracellular pathogens (as demonstrated for azithromycin [68]), and for P-glycoprotein and MRP2 in the liver, which contribute to its biliary elimination [69]. In humans, ketolide concentrations are ~ 10-times higher in the epithelial lining fluid (ELF) and ~ 100-times higher in alveolar macrophages than in the serum (**Table 2**). Telithromycin was also found to reach 6- and 1.6-times higher AUC in the nasal mucosa and in the ethmoid bone than in the plasma [70]. These properties suggest a favorable distribution as far as respiratory tract infections are concerned. Ketolides, like some hemisynthetic macrolides (roxithromycin, azithromycin), show a prolonged half-life allowing for their once-daily administration.

Pharmacodynamic animal models of pouch infection suggest that the best predictor for ketolide efficacy is the ([free AUC]/MIC) ratio, which needs to reach a value of at least 25 h^{-1} [71]. In a thigh infection model, a ([free AUC]/MIC) ratio > 200 h^{-1} is required to reach a maximal effect [72]. Due to the large distribution of the drugs out of the blood compartment, pharmacodynamic breakpoints based on serum concentrations are quite low, and close (or even lower for cethromycin) to the MIC values of target organisms (see **Tables 1** and **2**). Because target infections for ketolides are localized in the respiratory tract, one could, therefore, object that ([free AUC]/MIC) ratios reached in the ELF for extracellular bacteria and in macrophages for intracellular bacteria would be more representative. This is probably not the case, as preliminary studies with cethromycin using animal models of acute pneumonia show that a 100% survival can be achieved for ([free serum AUC]/MIC) ratios of 10 h^{-1}, corresponding to a ([free lung AUC]/MIC) ratio of 125 h^{-1}, but that success rate is reduced to 86% for

([free lung AUC]/MIC) ratio of 63 h^{-1} [73]. This suggests that breakpoints based on tissular accumulation only overestimate the true activity of the drugs. Likewise, despite their high cellular accumulation, macrolides and ketolides show disappointing efficacy in models of cells infected by *S. aureus*, probably due to their lack of bactericidal effect and to the defeating influence of acid pH on their activity [74]. They proved also less efficient than quinolones in models of intracellular infection by *Legionella* [37].

Moving now to human data, pharmacokinetic population analysis of patients receiving telithromycin for community-acquired pneumonia predicts that 90% eradication would be achieved for a ([total serum AUC]/MIC) ratio of 3.38 h^{-1}, with 100% target attainment rate up to MIC values of 1 mg/l for *S. pneumoniae, Moraxella catarrhalis* and *H. influenzae* [75]. In contrast, *in vitro* simulation of patients infected with macrolide-susceptible or macrolide-resistant *S. pneumoniae* suggests that eradication would require much higher ([free serum AUC]/MIC) ratios (25 h^{-1}; corresponding to a ([free ELF AUC]/MIC) ratio of ~ 180 h^{-1} [76]). The corresponding pharmacodynamic breakpoint would then be ~ 0.2 mg/l only. Success is accordingly observed for patients suffering from pneumonia caused by *S. pneumoniae* or *S. aureus* with lower MIC values (activity towards *H. influenzae* remains a matter of debate) [77]. On these bases, the European Committee on Antimicrobial Susceptibility Testing (EUCAST) has proposed as breakpoints for telithromycin S ≤ 0.25 mg/l and R > 0.5 mg/l ([78] definitive values will be published early in 2008). These breakpoints are considerably lower than the CLSI- and FDA-breakpoints, which will have an impact on the interpretation of the surveillance studies.

Telithromycin has a bioavailability of ~ 60% [79,80], allowing administration by the oral route. Quite surprisingly, however, only the oral formulation has been commercialized so far, which may constitute a limitation to its use in severely ill patients. The drug is eliminated both by renal and hepatic routes, so that it does not require dosage adjustments in patients with single organ insufficiency. A 50% dose reduction is, however, recommended for patients with major renal impairment (Cl_{cr} < 30 ml/min) and concomitant hepatic insufficiency. Because of side effects discussed later in this review, telithromycin is contraindicated in patients with previous history of hepatitis and/or jaundice associated with the use of macrolides.

As macrolides, ketolides are substrates and inhibitors for CYP3A4. Although this effect is much weaker than for erythromycin A, it may cause clinically relevant drug interactions [79], which are listed in **Table 3**. Case reports also document severe side effects in patients receiving telithromycin associated with verapamil [81] or digoxin [82]. Moreover, ketolides share with macrolides the capacity of prolonging QTc interval, which may increase the risk of *Torsades de pointes* in patients receiving other drugs affecting the electrocardiogram [83,85]. Drug interactions could also be mediated by the capacity of macrolides and ketolides to impair the activity of transporters, as demonstrated *in vitro* for pravastatin in hepatocytes [84]. Yet, the significance of this mechanism of drug interaction remains difficult to assess *in vivo*, due to the multiplicity of transporters with different specificities and orientations, and of their widespread localisation in the body.

4. Clinical efficacy and use

4.1 Approved clinical indications

Telithromycin is, so far, the only approved antibiotic among the ketolides. It received registration in 2001 in Europe and in 2004 in the US, with original indications including acute bacterial sinusitis, acute bacterial exacerbations of chronic bronchitis and mild-to-moderate (because of lack of intravenous formulation) community-acquired pneumonia in adults (no paediatric dosage available). In Europe, it also received approval for tonsillitis/pharyngitis caused by group A streptococci, as an alternative when β-lactams are not appropriate. In 2007, the use of telithromycin was restricted in the US to community-acquired pneumonia for safety reasons [85,86].

The next part of this section discusses these indications in light of what is known about telithromycin efficacy and safety, and the current guidelines.

Respiratory tract infections are the major reason for antibiotic prescribing in the community [87-89]. Thus, pharyngitis and sinusitis represent 1 – 2 and 0.2 – 0.4%, respectively of annual visits of adult patients to their general practitioners [90,91]. The prevalence of chronic obstructive pulmonary disease is increasing in industrialized countries, reaching ~ 5% in smokers [92,93]. The incidence of community-acquired pneumonia is ~ 2.3% of the US population, but higher in elderly or young people; it leads to patient hospitalisation in ~ 25% of the cases and remains a major cause of mortality [94,95].

Most often, the treatment of these infections is established on an empirical basis, in the absence of results from microbiologic diagnostic tests [96].

In such a situation, the choice of first-line drugs needs to take into account resistance trends. In particular, the prevalence of erythromycin resistance in *S. pneumoniae* is so high in several regions of the world that these drugs can no more be considered as first-line therapy in the absence of microbiologic data [97]. The emergence of multiresistant clones also further complicates drug selection.

4.2 Pharyngitis

The original European studies showed a similar efficacy of telithromycin compared with standard therapy for this indication, but these were either performed in countries of low erythromycin resistance, or/and included patients infected with macrolide-susceptible strains only [98-100]. This explains why telithromycin received approval in Europe as

Table 3. Drug interactions with ketolides (most of them have been documented so far for telithromycin).

Mechanism of drug interaction	Co-administered drug	Consequence	Ref.
CYP3A4 inhibition by co-administered drug	Ketoconazole, itraconzole	↑ C_{max} and ↑ AUC of telithromycin	[79]
CYP3A4 induction by co-administered drug	Rifampicin	↓↓ C_{max} and ↓↓ AUC of telithromycin	[79]
Inhibition of metabolism of co-administered drug by telithromycin	Simvastatin (CYP3A4)	↑↑ C_{max} and ↑↑ AUC	[79]
	Midazolam (CYP3A4)	↑↑ C_{max} and ↑↑ AUC	[79]
	Cisapride (CYP3A4)	↑ C_{max} and ↑ AUC	[79]
	Repaglinide (CYP3A4, CYP2C8)	↑ C_{max} and ↑ AUC	[79]
	Ethynylestradiol/levonorgestrel	↑ AUC levonorgestrel; no change in contraceptive efficacy	[79,80]
	Ergotamine	Not evaluated for ethical reason; risk of increased exposure and of ergotism	[85]
	Barbuturics Penytoïn Carbamazepine Cyclosporin Tacrolimus	Not evaluated; risk of increased exposure	[85]
	Metoprolol (CYP2D6)	↑ C_{max} and ↑ AUC	[147]
	Theophilline (CYP1A2)	↑ C_{max} and ↑ AUC	[79]
	Warfarine (CYP2C9)	Low ↑ C_{max} and low ↑ AUC	[79]
Reduction of drug metabolism due to change in gut microflora	Digoxine	↑ C_{max} and ↑ AUC	[79,80]
Decreased absorption	Sotalol	↓ C_{max} and ↓ AUC	[79]
Neutralization of gastric pH	Ranitidine	↓ C_{max} and ↓ AUC for cethromycin	[7,79]
Additive effect	Antiarythmic drugs (class IA and III) Cisapride Antipsychotics Fluoroquinolones Pentamidine Antimalarials Methadone	Prolongation of QTc interval, risk of *Torsades de pointes*	[85]

Single arrow: Maximum twofold change.
Double arrow: More than twofold change.

an alternative to β-lactams and as other macrolides. The use of telithromycin in pharyngitis is nevertheless disputable because it does not cover *S. pyogenes* with constitutive MLS_B phenotype (**Table 1**). Thus, telithromycin was not approved in the US for pharyngitis because the studies submitted at the FDA showed reduced efficacy compared with standard therapies using β-lactams, probably due to the inability of telithromycin to eradicate erythromycin-resistant *S. pyogenes* [83].

4.3 Acute sinusitis

Telithromycin 800 mg once daily during 5 days proved superior to azithromycin 500 mg/day during 3 days in the eradication of *S. pneumoniae* from the nasopharynx of patients with acute sinusitis, mainly due to the selection of erythromycin-resistant pneumococci during azithromycin therapy [101]. Several studies (reviewed by [83,102]) document that 5 days therapy with telithromycin is as efficient as 10 days therapy with β-lactams (amoxicillin/clavulanic acid or cefuroxime axetil) [103-107] or with moxifloxacin [108]. Note, however, that test-of-cure visits in all these studies took place after day 10, and that shorter treatments with comparators were not examined, preventing us from drawing conclusions relative to the comparison of treatment duration with these drugs. In fact, current guidelines recommend a treatment duration of 7 days with moxifloxacin and of 10 days with β-lactams in this indication [109,110].

4.4 Acute exacerbations of chronic bronchitis

Five days treatment with telithromycin was as efficient as 10 days treatment with amoxicillin/clavulanic acid or cefuroxime axetil [111,112], with again test-of-cure evaluation performed at day 17 – 21. The eradication rates were higher with telithromycin when the isolated pathogen was *S. pneumoniae* or *M. catarrhalis*, but lower when it was *H. influenzae*. Telithromycin treatment was also equivalent to 10 days therapy with clarithromycin b.i.d., and was associated with fewer unscheduled out-patient visits and hospitalisations

for respiratory-related causes [113]. A recent double-blind, randomized, placebo-controlled study also shows clear benefit on the respiratory function of telithromycin in acute exacerbations of asthma [114]. The mechanism of this effect remains unclear, as it is not related to the bacteriologic status of the patients. Possibly, an anti-inflammatory effect could take place and contribute to improve the patient status, as described for macrolides in patients suffering from cystic fibrosis, asthma or panbronchiolitis [115,116].

4.5 Community-acquired pneumonia

Four randomized, double-blind [117-120] and 4 open-label [121-123] studies were supporting the FDA dossier of telithromycin [83]. They compared 800 mg/day telithromycin for 7 – 10 days with clarithromycin (500 mg b.i.d.), amoxicillin (1000 mg three times a day) for 10 days, or trovafloxacin 200 mg once daily for 7 – 10 days. These studies excluded patients with severe symptoms and who needed parenteral antibiotics. A similar cure rate was reached in telithromycin-treated patients as in comparator groups, including in patients aged > 65 years, with bacteremia or with a Fine score > III [102,124]. Bacterial eradication rate was ~ 90% in the telithromycin groups, including for patients infected by penicillin- and erythromycin-resistant pneumococci or by atypical pathogens [102]. Note, however, that the proportion of erythromycin-resistant pneumococci in these studies was quite low (~ 5%), which prevented demonstrating an advantage of telithromycin over macrolides.

In the last release of the Infectious Diseases Society of America guidelines [125], the place for telithromycin is not specifically addressed: '*At present, the committee is awaiting further evaluation of the safety of telithromycin by the US Food and Drug Administration before making its final recommendation regarding this drug*.' Macrolides appear as first-line therapy in out-patients with no co-morbidities or risk factors for drug-resistant pneumonia. In the European Respiratory Society guidelines [126], macrolides are proposed as an alternative to β-lactams, but the authors state that '*clinical experience with telithromycin is too limited to make specific recommendations*.'

5. Safety issues

In Phase II/Phase III studies, telithromycin was judged as safe as its comparators [83,124,127], with most frequent side effects including diarrhoea, nausea, headache (5 – 10%), dizziness, vomiting, loose stools, dysgeusia (1.5 – 4%) and reversible increase in transaminase levels (0.2 – 2%) and hepatitis (0.07%).

Postmarketing surveillance studies, however, have evidenced three cases of severe hepatotoxicity, one of which was fatal and another which required liver transplantation [128]. On these bases, the European Medicines Agency (EMEA) asked the sponsor in January 2006 to add stronger warnings about potential liver problems to the telithromycin Summary of Product Characteristics (SPC [labeling]). The EMEA statement was the following: '*Cases of serious acute hepatitis, including liver failure, some of which were fatal, have been reported to and assessed by the EMEA in the context of the continuous monitoring of the safety of KETEK. The reported serious liver reactions started during or immediately after treatment with KETEK and were, in most cases, reversible after use of this product was discontinued*' [129]. Likewise, the FDA recommended in May 2006 to add a 'black box' warning to the KETEK labeling, stating that '*severe, life-threatening, and in some cases fatal liver toxicity has been reported in patients taking KETEK*' [86]. As a consequence, in February 2007, the FDA and the sponsor agreed on an updated label for telithromycin, which narrowed its use to community-acquired pneumonia. The other previously approved indications were thus dropped in the US. This restrictive measure has not been applied so far in Europe. A question here is whether the safety data from the study submitted to FDA registration had not been falsified in favor of the drug and whether FDA should not have reacted earlier, based on the first reports of toxicity [130,131].

And the story is not yet finished. In February 2007, a new warning box was added in the KETEK labeling [85,86], stating that the drug is '*contraindicated in patients with myasthenia gravis. There have been reports of fatal and life-threatening respiratory failure in patients with myasthenia gravis associated with the use of KETEK*.' Of note, some cases were already reported as early as in 2003, forcing Aventis to send a warning letter to prescribers (see [132] for review on this side effect of telithromycin). Phase IV studies also evidenced rare cases of visual disturbances (mainly blurred vision in young ladies) and loss of consciousness, including some cases associated with vagal syndrome.

Last but not least, telithromycin has the potential to prolong the QTc interval of the electrocardiogram in some patients. Cases of *Torsades de pointes* have been reported postmarketing, which calls for caution in patients receiving class IA or class III antiarythmic drugs or other drugs susceptible to prolong QTc interval (including cisapride, antipsychotics, fluoroquinolones, pentamidine, antimalarials, arsenic trioxide, and methadone [133]) as well as in patients with ongoing proarrhythmic conditions such as uncorrected hypokalemia or hypomagnesemia, or clinically significant bradycardia [85].

6. Expert opinion

The main bacterial target of ketolides is *S. pneumoniae*, the key pathogen in respiratory tract infections. Erythromycin-resistance in this bacterial species is globally increasing [97], most likely in relation to the wide use of macrolides in the community [134,135]. Prevalence of erythromycin resistance seems also higher in countries using preferentially azithromycin over other macrolides [136], probably in relation with the low serum levels of azithromycin.

In such a context, ketolides appear as the most obvious successors to macrolides for community-acquired infections

where *S. pneumoniae* can be considered as the most likely causative organism and in areas where resistance to erythromycin A is high. Their oral route and once-daily dosage make them also highly suitable for use in the community. These properties also justify the use of telithromycin as alternative to β-lactams in respiratory tract infections (patients intolerant to β-lactams; risk of infection by a penicillin-resistant strain). What remains less clear so far is the respective positioning of ketolides versus the so-called 'respiratory' fluoroquinolones [125,126]. The main drawbacks of fluoroquinolones, often presented to justify a limitation in their use in respiratory tract infections, include a (too) broad spectrum of activity, an easy selection of resistance, and the risk of multiple side effects [137]. Similar weaknesses may, however, also counterbalance the advantages of ketolides enumerated above. First, large-scale use will certainly favor the emergence of resistance, which has already begun to be described (the low serum levels of ketolides, and of cethromycin in particular, may reproduce the situation seen with azithromycin). Second, the occurrence of rare, but serious, side effects may lead to restrictions and/or voluntary withdrawal, as seen with several fluoroquinolones in the past [137]. As the interest of using antibiotics in non-severe upper respiratory tract is debatable, the decision of keeping telithromycin for truly worthy indications such as pneumonia seems wise, especially if it can be combined with pro-active surveillance studies aiming at documenting the susceptibility of the causative organisms to this antibiotic. Forthcoming ketolides will certainly be examined with caution with respect to these issues.

In a broader context, the example of ketolides, as well as that of fluoroquinolones, should trigger industry, guideline makers and authorities to reanalyze the overall process of antibiotic discovery, registration and usage, while maintaining it economically viable and susceptible to meet the rising risks of multi-drug resistance.

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