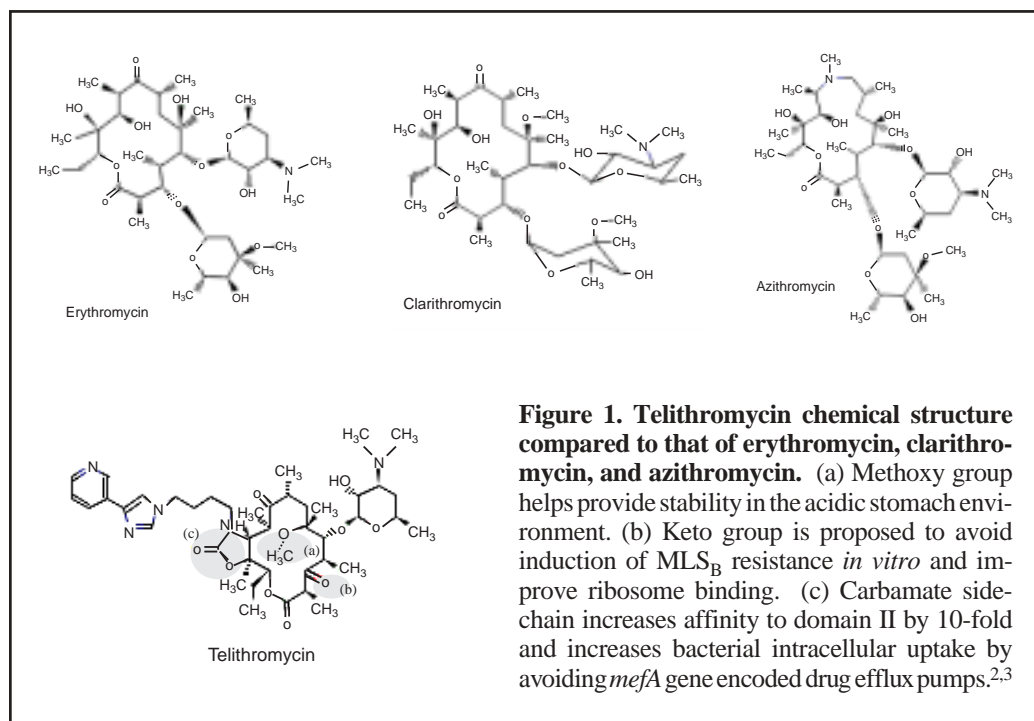


Telithromycin, the First FDA-Approved Ketolide: Just Another Antibiotic?

By Oanh H. Dang, Pharm.D.

The greatest risk factor for resistant microorganisms is recent antibiotic use.¹ Antibiotics with novel mechanisms of action are constantly needed to counter emerging resistance to existing penicillins, macrolides, cephalosporins, and fluoroquinolones. Common mechanisms of bacterial resistance include target site changes, reduced bacterial cell uptake via increased drug efflux, and the production of inactivating enzymes.² An optimal antibiotic would effectively eradicate the microorganism and lower or avoid the induction of resistance.³ Telithromycin (Ketek[®]) is the first ketolide antimicrobial agent to be marketed in the United States. It is FDA approved for use in the treatment of respiratory tract infections including acute bronchial sinusitis, acute exacerbation of chronic bronchitis, and mild-to-moderate community-acquired pneumonia caused by common and atypical respiratory pathogens. This article will examine whether telithromycin possesses the properties of an optimal antibiotic and will compare and contrast telithromycin to macrolide and fluoroquinolone antibiotics.



Telithromycin is a macrolide derivative that is most structurally related to clarithromycin (see Figure 1). Telithromycin and macrolide antibiotics both inhibit bacterial protein synthesis by binding to domain II and V of the 50S subunit of 23S ribosomal RNA. However, unlike macrolides which bind only weakly to domain II, the presence of the carbamate side-chain causes telithromycin to have a strong interaction with (continued on page 26)

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The spectrum of activity for telithromycin encompasses: *S. pneumoniae* (including penicillin- and macrolide-resistant strains), *S. aureus*, *H. influenzae*, *M. catarrhalis*, *C. pneumoniae*, and *M. pneumoniae*.

domain II. Thus, telithromycin retains activity against macrolide-lincosamide-streptogramin B (MLS_B) resistance which is mediated by methylation of the domain V binding site by microbial methylase enzymes produced from *erm* genes.²⁻⁴

Telithromycin concentrates in lung tissue (bronchial mucosa, epithelial lining fluid, and alveolar macrophages) thereby enhancing its activity against respiratory tract pathogens.⁵ The spectrum of activity of telithromycin includes *Streptococcus pneumoniae* (including penicillin- and macrolide-resistant strains), *Staphylococcus aureus*, *Haemophilus influenzae*, *Moraxella catarrhalis*, *Chlamydomphila pneumoniae*, and *Mycoplasma pneumoniae*.⁵ Table I illustrates the minimal inhibitory concentration (MIC) breakpoints that are used to categorize *S. pneumoniae*, *H. influenzae*, and *S.*

aureus as susceptible, intermediate, or resistant to telithromycin⁶, and the lowest concentrations of telithromycin that inhibit 50% and 90% of bacterial growth are compared to that of commonly used macrolides and fluoroquinolones in Table II. The pharmacokinetic properties of telithromycin are shown in Table III.

Table I: MIC Breakpoints for Telithromycin (mcg/mL)⁶

Organism	Susceptible	Intermediate	Resistant
<i>S. pneumoniae</i> <i>S. aureus</i>	≤ 1	2	≥ 4
<i>H. influenzae</i>	≤ 4	8	≥ 16

Table II: MIC values (in mcg/mL) for telithromycin, macrolides, and fluoroquinolones against isolates of *S. pneumoniae* and *H. influenzae*.⁷

Organism		Azithromycin		Clarithromycin		Moxifloxacin*		Levofloxacin		Telithromycin	
		MIC ₅₀	MIC ₉₀	MIC ₅₀	MIC ₉₀	MIC ₅₀	MIC ₉₀	MIC ₅₀	MIC ₉₀	MIC ₅₀	MIC ₉₀
<i>S. pneumoniae</i>	Penicillin ^S (n = 6183)	0.12	0.25	0.06	0.06	NT	NT	1	1	≤ 0.015	0.03
	Penicillin ^I (n = 1266)	4	≥ 512	1	≥ 512	NT	NT	1	1	0.03	0.5
	Penicillin ^R (n = 2654)	16	≥ 512	8	≥ 512	NT	NT	1	1	0.25	1
	Erythromycin ^S (n = 6950)	0.12	0.25	0.06	0.06	NT	NT	NT	NT	≤ 0.015	0.03
	Erythromycin ^R (n = 3133)	16	≥ 512	8	≥ 512	NT	NT	NT	NT	0.25	1
<i>H. influenzae</i>	B-lactamase (-) (n = 1941)	2	4	8	16	≤ 0.03	≤ 0.03	≤ 0.06	≤ 0.06	2	4
	B-lactamase (+) (n = 769)	2	4	8	16	≤ 0.03	≤ 0.03	≤ 0.06	≤ 0.06	2	4

S = Susceptible, I = Intermediate, R = Resistant phenotypes; (-) = Negative, (+) = Positive; NT = not tested

*In the global PROTEKT surveillance program for the U.S. (n=337), moxifloxacin's MIC₅₀ was 0.12 and MIC₉₀ was 0.25 for all isolates of *S. pneumoniae*.⁸

Cure rates associated with telithromycin are similar to those of other antibiotics currently used to treat respiratory infections.

Telithromycin's role is essentially limited to an alternative option for the treatment of acute bacterial sinusitis, acute exacerbation of chronic bronchitis, and mild to moderate community-acquired pneumonia.

Randomized, double-blinded trials in adults have shown telithromycin, at a daily dose of 800mg, to be similar in efficacy to other antibiotics currently used to treat respiratory infections (see Table IV).⁹⁻¹⁷ Currently there are no studies directly comparing telithromycin to azithromycin and only one trial comparing telithromycin to a fluoroquinolone. In clinical trials the most common adverse events attributed to telithromycin were diarrhea and nausea. Rare but concerning adverse effects reported with telithromycin have included QT prolongation, exacerbation of myasthenia gravis, elevated liver function tests, and pseudomembranous colitis. Telithromycin has been reported to delay accommodation, the ability of the eyes to adjust when observing objects at varying distances, resulting in blurry vision, difficulty focusing, or diplopia.¹³ Such visual disturbances are said to occur in 2.1% of women less than 40 years of age and most commonly occur after the first or second dose. In some cases, the visual adverse effects resolved with continued therapy; but in other cases, they persisted for the duration of treatment. Post-marketing reports have identified rare but serious cases of angioedema, anaphylaxis, atrial arrhythmias, and hepatic dysfunction.⁵

As for erythromycin, also noteworthy with telithromycin are drug interactions. Given

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Table III: Telithromycin Pharmacokinetics^{5,13}

Oral Bio-availability	57%
T _{max}	1 hour post dose
C _{max} (mcg/mL)	1.9 (single 800mg dose); 2.27 (at steady state)
Protein binding	60-70%
Metabolism	70% of dose is metabolized; ~50% by CYP3A4 and 50% by other isoenzymes (including CYP2D6)
Half-life	9.8 hours
Elimination	7% excreted unchanged in feces by biliary and/or intestinal secretion; 13% excreted unchanged in urine

Telithromycin is a major substrate and potent inhibitor of cytochrome P450 3A4, and minor 2D6 substrate, predisposing it to many drug interactions

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that telithromycin is a major substrate and potent inhibitor of cytochrome P450 3A4 and a minor CYP2D6 substrate, it is predisposed to many drug interactions (see Table V). Due to an increased risk of QT prolongation, telithromycin is specifically contraindicated in patients taking cisapride. In comparison with azithromycin, a minor substrate and weak inhibitor of CYP3A4, and fluoroquinolones, which do not undergo CYP3A4 metabolism, telithromycin's potential for drug interactions is significantly greater.

Telithromycin belongs to a new class of antibiotics indicated for the treatment of respiratory tract infections, but the vital question is whether or not it offers any advantage compared to other available antibiotics? First, at the molecular level, telithromycin's mechanism of action confers benefits in comparison to macrolides by overcoming bacterial resistance with its increased binding affinity at targeted sites, decreased susceptibility to efflux pumps, and possible avoidance of inducing MLS_B resistance.³ Thus, telithromycin has potential as a fluoroquinolone-sparing agent when macrolide-resistant *S. pneumoniae* is a concern. Second, once daily dosing is a feature of telithromycin regimens that may improve patient adherence to therapy; however, this feature is also shared by azithromycin and the fluoroquinolones. Third, the GI tolerability of telithromycin is similar to clarithromycin;¹⁶

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Table IV: Randomized Double-Blind Studies of Telithromycin

	Reference	Age range years (median)	N	Telithromycin Dosing Schedule	Comparator Dosing Schedule	Clinical Cure: Telithromycin vs. Comparator
Sinusitis	Buchanan ⁹	14-84 (40)	356	800mg po daily x 5 days	Cefuroxime 250mg po BID x 10 days	85.2% vs. 82%
	Luterman ¹⁰	16-84 (39)	607	800mg po daily x 5 or 10 days	Amoxicillin/clavulanate 500/125mg po TID x 10 days	75.3% (5-day) or 72.9% (10-day) vs. 74.5%
Bronchitis	Aubier ¹¹	18-84 (61)	320	800mg po daily x 5 days	Amoxicillin/Clavulanate 500/125mg po TID x 10 days	81.3% vs 78.1%
	Zervos ¹²	19-97 (50)	373	800mg po daily x 5 days	Cefuroxime 500mg po BID x 10 days	86.4% vs 83.1%
	Labeling ¹³	18-95 (not specified)	552	800mg po daily x 5 days	Clarithromycin 500mg po BID x 10 days	85.8% vs 89.2%
Pneumonia	Hagberg ¹⁴	16-88 (41)	404	800mg po daily x 10 days	Amoxicillin 1000mg po TID x 10 days	94.6% vs 90.1%
	Tellier ¹⁵	18-92 (43)	575	800mg po daily x 5 or 7 days	Clarithromycin 500mg po BID x 10 days	89.3% (5-day) or 88.8% (7-day) vs. 91.8%
	Pullman ¹⁶	18-99 (46)	204	800mg po daily x 7-10 days	Trovafloxacin 200mg po daily x 7-10 days	90% vs 94.2%
	Hagberg ¹⁷	18-92 (45)	416	800mg po daily x 10 days	Clarithromycin 500mg po BID x 10 days	88.3% vs 88.5%

Table V: Telithromycin Drug Interactions¹³

Concomitant Drug	Likely Mechanism	Potential Effects	Recommendation
Carbamazepine, cyclosporine, phenytoin, sirolimus, tacrolimus	CYP 3A4 induction of telithromycin metabolism	↓ telithromycin effects	Avoid combination
Digoxin	P-glycoprotein efflux pump inhibition decreases renal tubular secretion of digoxin	↑ digoxin levels	Monitor digoxin levels
Ergot alkaloids (ergotamine, dihydroergotamine)	Not known; Potential interaction extrapolated from macrolides	Acute ergot toxicity	Avoid ergotamine alkaloid co-administration
Metoprolol	CYP 2D6 substrate; telithromycin competes for metabolism	↑ beta blocker effects	Monitor for bradycardia
Midazolam	CYP 3A4 substrate; telithromycin competes for metabolism	↑ midazolam effects	Use caution with co-administration
Rifampin	CYP 3A4 induction of telithromycin metabolism	↓ telithromycin effects	Although unstudied, consider telithromycin dose ↑
HMG CoA Reductase Inhibitors	CYP 3A4 substrates; telithromycin competes for metabolism	↑ risk of rhabdomyolysis	Temporarily d/c simvastatin, lovastatin, atorvastatin
Sotalol	↓ absorption	↓ sotalol effects	Monitor for arrhythmias; consider sotalol dose ↑
Theophylline	Co-administration may worsen gastrointestinal effects	↑ gastrointestinal effects	Take 1 hour apart

Pharmacy & Therapeutics Committee Actions

Formulary Additions	Dosage Form(s), Strength(s), & Cost [‡]	Therapeutic Classification	Use	Usual Adult Starting Dose*
Paclitaxel protein-bound particles (Abraxane)	Injection: 100mg	Mitotic Inhibitor	Breast cancer	260mg/m ² q 3 weeks
	The Committee voted to limit use to outpatient oncology patients who have failed Taxol [®] because of disease progression or anaphylaxis and who have prior 3rd-party payor authorization. Inpatient use requires approval from the Medical Director.			
Pegaptanib (Macugen)	Injection: 0.3mg	Vascular endothelial growth factor antagonist	Neovascular age-related macular degeneration	0.3mg q 6 weeks
	The Committee voted to require prescriber-obtained authorization from patient's insurer prior to initiating therapy.			
Other Actions				
Citalopram (Celexa)	Added to the UW Medicine Preferred Drug Formulary (uw-PDF).			

* Refer to product labeling for full prescribing information. ‡ Contact pharmacy for information on drug costs.

Table VI: UW Medicine Outpatient Charge

Regimen	Cost
Azithromycin 500mg po, then 250mg q day x 4	\$53.20
Clarithromycin 500mg po BID x 10 days	\$69.50
Levofloxacin 500mg po q day x 10	\$51.35
Moxifloxacin 400mg po q day x 10	\$75.05
Telithromycin 800mg (2 x 400mg) po q day	\$67.44 (5-days); \$130.69 (10-days)

however, the risks may outweigh the benefits in patients predisposed to visual disturbances, liver enzyme elevations, or prolonged QT syndrome. Finally, relative to azithromycin and the fluoroquinolones, the drug-drug interaction potential of telithromycin is considerable.

In summary, telithromycin is the first, but not likely the last, ketolide antibiotic to be cleared for marketing in the U.S., and other ketolides are currently under study. In light of efficacy that is similar to the current standard of care and a safety profile that may be tipped slightly towards more risk, telithromycin's current role in therapy is essentially limited to a second- or third-line alternative for the treatment of sinusitis, bronchitis, and community-acquired pneumonia. Thus, due to the lack of evidence for superior risk-to-benefit and cost-to-benefit ratios compared to current formulary options for respiratory infections, telithromycin was considered for, but not added to, the UW Medicine Drug Formulary.

References available upon request.

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