

## The Evolution of Antimicrobial Agents Used for the Management of CARTIs: A Focus on a New Class of Antimicrobials—the Ketolides

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Numerous issues exist surrounding the management of community-acquired respiratory tract infections (CARTIs). Most CARTIs are initially treated empirically, preferably based on guidelines developed by professional organizations,<sup>1,2</sup> but realistically the selection is often determined by the physician's habitual practice pattern—a practice pattern based on successful past treatment experiences.<sup>3</sup> Unfortunately, the use of inadequate empiric therapies for CARTIs will inevitably result in a progressive increase in antibiotic resistance among CARTI pathogens. An increase in multi-drug resistant *Streptococcus pneumoniae* (MDRSP) has already been documented.<sup>4</sup>

Other factors of concern include the failure of some antibiotic classes to cover the most common pathogens for CARTIs, bacteriostatic activity rather than bactericidal effect against CARTI pathogens, the effect of prolonged exposure to subinhibitory levels of an antibiotic, and the potential for collateral damage caused by a spectrum of antibiotic activity that also targets non-respiratory tract organisms.

The approval of the first member of a new class of antibiotics in the United States, the ketolides, will provide healthcare practitioners a new choice for the treatment of CARTIs. Members of the ketolide class possess numerous attributes that compare favorably with existing empiric therapies. These attributes include bactericidal activity against the most prevalent CARTI pathogens; excellent tissue penetration; effectiveness against infections caused by multidrug-resistant organisms; a tailored spectrum of activity; and, for some patients, a shorter course of therapy than most of the current

antibiotic regimens. There are several ketolides in various stages of clinical development, including telithromycin, RWJ-415663, CP-654743, and TE-802. The availability of a new class of antibiotics will prompt the pharmacy and therapeutic committees of health plans to consider including a ketolide on the formulary.

The goal of this article is to provide managed care and other formulary decision makers with an overview of the chemical characteristics of the ketolide class; to compare the characteristics of ketolides and other classes of antimicrobials; and to provide a review of the safety and efficacy research currently conducted for ketolides now available in the United States. Basic to formulary decisions is an understanding of the defining characteristics of a new drug class and the differentiating attributes of the agents within that class.

### The Ketolides

**Chemical Structure.** Derived from erythromycin A, ketolides retain the 14-member macrolactone ring and the D-desosamine sugar at position 5. However, ketolides have a number of structural differences that improve on both the activity and the pharmacokinetics of the macrolides. The only structural modification necessary to classify a compound as a ketolide is the replacement of the L-cladinose moiety with a 3-ketone. The earliest macrolides quickly degrade within an acidic environment, resulting in erratic absorption and gastric irritation.<sup>5</sup> The removal of the L-cladinose moiety maintains the improved acid stability of second-generation macrolides by avoiding ketalization. Replacement with the

3-ketone enables ketolides to overcome the most common forms of bacterial resistance, macrolide-efflux (*mef*)-encoded efflux and inducible MLS<sub>B</sub> resistance.<sup>6,7</sup>

Other molecular characteristics also improve ketolide activity. Telithromycin possesses a carbamate extension with an alkyl-aryl group at positions 11/12; this extension enhances ribosomal binding affinity, allowing telithromycin to remain potent against erythromycin-resistant strains.<sup>6</sup> Telithromycin, HMR-3004, and HMR-3787 also have a 6-methoxy group, which further improves acid and molecular stability by preventing ketalization.<sup>8</sup>

**Mechanism of Action.** Like macrolides, ketolides exert their antimicrobial activity by preventing the translation of bacterial messenger ribonucleic acid (RNA), which inhibits ribosome assembly and protein synthesis.<sup>9</sup> In susceptible bacteria, ketolides and macrolides bind to sites on the 23S ribosomal RNA (rRNA) of the larger 50S ribosomal subunit. Ketolides and macrolides both bind primarily to the domain V contact site in 23S rRNA.<sup>10</sup> Both macrolides and ketolides also interact with the binding domain II on 23S rRNA, but do so quite differently.<sup>6,10,11</sup> Ketolides that possess a carbamate extension at positions 11/12 allows for strong binding to domain II, whereas the macrolides form a weak bond to domain II.<sup>7,10</sup> Further, although the binding of ketolides to domain II blocks a specific nucleotide (A752) on that domain from ribosomal assembly,<sup>10,12</sup> macrolide binding to domain II renders the base of A752 more accessible to chemical modification, likely because of allosteric effects.<sup>6</sup> Overall, telithromycin has been demonstrated to bind to bacterial ribosomes with 6 to 10 times the binding affinity of macrolides.<sup>6,10</sup> The interaction of the carbamate extension with domain II is believed to cause the enhanced binding affinity.<sup>6</sup>

Two of the main mechanisms of resistance to macrolides are target-site alteration and active drug efflux.<sup>13</sup> Target-site alteration is encoded by erythromycin resistance methylase (*erm*) genes, and is called MLS<sub>B</sub> resistance.<sup>6,14</sup> This *erm*-mediated resistance alters the ribosomal structure on

domain V<sup>6</sup> and reduces binding affinity for the antibiotic.<sup>14</sup> The binding of telithromycin at domain II allows telithromycin to maintain antibiotic activity against bacteria that have base mutations at domain V.<sup>11,15-17</sup> In resistance caused by active drug efflux, the *mef* gene codes for membrane-bound proteins to pump 14- and 15-membered macrolides out of bacterial cells.<sup>18</sup> This type of resistance is not seen with ketolides, 16-membered macrolides, lincosamides, or streptogramins.<sup>5</sup>

### **Telithromycin: The First Ketolide Approved for Use in the United States**

Although there are numerous compounds in the ketolide class in the preclinical or clinical trial phase of development, telithromycin is the only ketolide approved for use in the United States. Telithromycin is indicated for the treatment of acute exacerbations of chronic bronchitis (AECB), acute bacterial sinusitis (AS), and community-acquired pneumonia (CAP) of mild-to-moderate severity caused by susceptible strains of designated microorganisms in patients  $\geq 18$  years of age.<sup>19</sup>

### **In Vitro Activity**

**Gram-positive Pathogens.** Telithromycin has demonstrated effective in vitro activity against gram-positive pathogens responsible for respiratory tract infections (RTIs).<sup>20</sup> Telithromycin has good activity against *S pneumoniae*, regardless of penicillin or macrolide susceptibility. The minimum inhibitory concentration (MIC) break points indicating susceptibility, intermediate susceptibility, and resistance to telithromycin are  $<1$ , 2, and  $\geq 4$  mcg/mL for *S pneumoniae*.<sup>19</sup> Against penicillin-susceptible strains, telithromycin has an in vitro MIC<sub>90</sub> of 0.015 mcg/mL.<sup>21</sup> Telithromycin MIC<sub>90</sub> values were low against strains of *S pneumoniae* that were penicillin resistant (0.25-1.0 mcg/mL) and/or erythromycin resistant (0.06-1.0 mcg/mL).<sup>22-27</sup> Even against *S pneumoniae* isolates with *ermB* resistance or the *mef* gene, the telithromycin MIC<sub>90</sub> remained low (each 0.06 mcg/mL).<sup>28</sup>

During the first year (2000-2001) of the Prospective Resistant Organism Tracking and Epidemiology for the Ketolide Teli-

thromycin (PROTEKT) study, over 10 000 *S pneumoniae* isolates were collected in the United States. Of these, 99.7% were susceptible to telithromycin.<sup>4</sup> During the second year of the study (2001-2002), nearly 40% of the *S pneumoniae* isolates exhibited resistance to one or more of the antibacterials tested. Of these resistant isolates, 75% were MDRSP. Telithromycin was highly effective against MDRSP, with 99.5% of the isolates susceptible to telithromycin at  $\leq 1$  mcg/mL.<sup>29</sup>

Telithromycin also demonstrates activity against methicillin-susceptible *Staphylococcus aureus* (MIC<sub>90</sub>:  $\leq 0.25$  mcg/mL).<sup>30-32</sup>

**Gram-negative Pathogens.** Telithromycin has demonstrated good in vitro activity against gram-negative pathogens responsible for RTIs. The MIC break points indicating susceptibility, intermediate susceptibility, and resistance to telithromycin are  $\leq 4$ , 8, and  $\geq 16$  mcg/mL for *Haemophilus influenzae*.<sup>19</sup> In the first year of the PROTEKT study, more than 2700 isolates of *H influenzae* were collected; an MIC<sub>90</sub> of 4 mcg/mL was obtained for telithromycin, demonstrating susceptibility.<sup>4</sup> *H influenzae* susceptibility to telithromycin is unaffected by beta-lactamase production or ampicillin resistance.<sup>4,30,33-35</sup>

Against *Moraxella catarrhalis*, telithromycin MIC<sub>90</sub> values range from 0.03 to 0.125 mcg/mL.<sup>26,31-33,35,36</sup> *M catarrhalis* susceptibility was unaffected by beta-lactamase production.<sup>34,35</sup>

**Atypical and Intracellular Organisms.** Of importance (especially when treatment is initiated in the absence of culture data), telithromycin is potent against *Mycoplasma pneumoniae* and *C pneumoniae*. Low MIC<sub>90</sub> ranges of telithromycin have been reported for *M pneumoniae* ( $\leq 0.015$  mcg/mL) and *C pneumoniae* ( $\leq 0.025$  mcg/mL).<sup>37-41</sup>

### Pharmacokinetics

**Absorption and Distribution.** The absolute bioavailability of a single 800-mg dose of telithromycin is 57%; this was observed in both young (18-40 years) and older (65-85 years) subjects.<sup>42</sup> Plasma concentrations and pharmacokinetic param-

eters of telithromycin were not altered by a high-fat breakfast; therefore, telithromycin may be administered without regard to meals.<sup>43</sup> Steady-state concentrations of telithromycin are reached after 2 to 3 days of repeated administration; at steady state, an 800-mg dose of telithromycin produces a mean peak plasma concentration (C<sub>max</sub>) of 2.27 mg/L within 1 hour and an area under the 24-hour plasma concentration curve (AUC<sub>24</sub>) of 12.5 mcg\*h/mL.<sup>19,44</sup>

Telithromycin 800 mg once daily achieves high drug concentrations in bronchial tissue, epithelial lining fluid, and alveolar macrophages.<sup>36,45-47</sup> Telithromycin concentrations at these sites remained above the telithromycin MICs for most of the major respiratory pathogens throughout the 24-hour administration period.<sup>36,46</sup> A number of in vitro studies have demonstrated the preferential uptake of telithromycin by polymorphonuclear neutrophils.<sup>48,49</sup> High telithromycin concentrations were also seen in white blood cells,<sup>50</sup> which may contribute to the delivery of telithromycin to sites of infection.

**Metabolism and Elimination.** Cytochrome P450 3A4 and noncytochrome P450 isoenzymes metabolize approximately 70% of a telithromycin dose.<sup>19</sup> There are 4 major metabolites, one of which (RU 76363, an N-oxide pyridine derivative) has demonstrated antibacterial activity, but at 6% to 25% of that of telithromycin.<sup>51</sup>

Telithromycin is eliminated by various pathways, with 7% excreted unchanged in the feces, 13% excreted unchanged in urine, and 37% metabolized in the liver.<sup>19</sup> Telithromycin has an overall terminal half-life of 9.8 hours.<sup>44</sup>

**Dosing in Special Populations.** There were only minor differences in the pharmacokinetics of telithromycin in elderly patients and in patients with moderate-to-severe hepatic impairment; no dose adjustment is required in these patient groups. In patients with severe renal failure (CL<sub>CR</sub> <30 mL/min) who received once-daily telithromycin for 5 days, mean steady-state C<sub>max</sub> and AUC<sub>24</sub> were 1.5 and 2.0 times higher, respectively, than normal volunteers.<sup>52</sup> How-

ever, the dosage of telithromycin in patients with severe renal impairment has not been established.<sup>19</sup>

### Pharmacodynamics

In the previous article, Dr Nicolau reports that bactericidal antibiotics have a lower propensity to induce resistance compared with bacteriostatic agents, as bactericidal antibiotics quickly eradicate susceptible pathogens. In vitro studies have been performed to determine the pharmacodynamics of telithromycin. The rate and extent of killing in *S pneumoniae* were examined at a concentration corresponding to the unbound 2-hour level in serum following administration of a dose of 800 mg (0.6 mg/L) of telithromycin.<sup>53</sup> Telithromycin demonstrated excellent bactericidal activity against *S pneumoniae*, exhibiting an extremely fast kill rate (3 log<sub>10</sub> CFU [colony forming units]/mL after 1 hour) in all strains tested, regardless of whether the strain was penicillin susceptible or not. Telithromycin exhibits a slower kill rate against *H influenzae*, but is bactericidal at 24 hours at a concentration of 4 times the MIC.<sup>54</sup> In addition, telithromycin has been determined to exhibit concentration-dependent killing.<sup>55</sup>

### Drug Interactions

The absorption of telithromycin is unaffected by agents that alter the gastric pH of the stomach; coadministration of ranitidine or magnesium/aluminum hydroxides did not affect the pharmacokinetics of telithromycin.<sup>19,56</sup>

Because telithromycin is a competitive inhibitor of cytochrome P450 CYP 3A4, coadministration of telithromycin with a drug that is a CYP 3A4 inhibitor or substrate may increase the plasma concentrations of the coadministered drug. Coadministration of ketoconazole and itraconazole with telithromycin resulted in a 1.98-fold and 1.53-fold increase in AUC<sub>24</sub> for telithromycin, respectively. Because there were no significant changes to the QT<sub>c</sub> interval from baseline for either product, telithromycin dose adjustment is not necessary.<sup>19,57</sup> Coadministration of telithromycin and cisapride resulted in a 95% increase in the cisapride steady-state C<sub>max</sub>; coadministration of

cisapride with telithromycin is contraindicated, as cisapride is known to increase the potential for QT interval irregularities and ventricular arrhythmias.<sup>19</sup> Coadministration of telithromycin with pimozone is also contraindicated due to the risk of increased plasma concentrations of pimozone.<sup>19</sup>

An 8.9-fold increase in AUC and a 5.3-fold increase in C<sub>max</sub> of simvastatin were seen when coadministered with telithromycin.<sup>19</sup> Similar interactions are also possible with other hydroxymethyl glutaryl coenzyme A reductase inhibitors metabolized by CYP 3A4; therapy with simvastatin, lovastatin, or atorvastatin (but not pravastatin, fluvastatin, or rosuvastatin) should be suspended during telithromycin therapy.<sup>19,58</sup>

Coadministration of telithromycin with intravenous and oral midazolam led to 162% and 511% increases in the AUC of midazolam, respectively.<sup>18</sup> For midazolam and the other benzodiazepines metabolized by CYP 3A4 (such as triazolam), caution is recommended, and dosage adjustments should be made as necessary.<sup>19</sup>

Coadministration of telithromycin and digoxin led to a 1.4-fold increase in the AUC of digoxin.<sup>59</sup> Although there were no significant changes in electroencephalogram patterns or signs of digoxin toxicity, monitoring of patients for symptoms of digoxin toxicity is recommended.<sup>19</sup> Theophylline, paroxetine, warfarin, and oral contraceptives were all shown to be unaffected to any significant degree by telithromycin therapy.<sup>19,59-61</sup> Because coadministration of theophylline with telithromycin may increase gastrointestinal adverse events (ie, nausea, vomiting), it is recommended that the drugs be administered at least 1 hour apart to decrease the likelihood of these events.<sup>19</sup>

### Clinical Efficacy

The phase 3 clinical program for telithromycin included 14 trials conducted in the United States, South America, Europe, Australia, and South Africa.<sup>59,62-74</sup> The therapeutic efficacy of telithromycin 800 mg once daily for AS, AECB, or CAP was evaluated. All comparative studies were double blind; the objective of the trials was to demonstrate equivalence with comparator antibiotic(s). The primary end point in most



studies was clinical outcome in the per-protocol population at the test of cure visit (days 17-24). Clinical cure was defined as either improvement or a return to the patient's preinfection status, or improvement with residual symptoms but no need for subsequent antimicrobial therapy. A satisfactory bacteriological outcome was defined as the eradication or presumed eradication of the offending pathogen at the test of cure visit among bacteriologically evaluable per-protocol patients.

**Acute Bacterial Sinusitis.** The efficacy of telithromycin for the treatment of AS has been studied in 3 trials with a total of 1333 patients. In these trials, telithromycin 800 mg once daily for 5 days was compared with 10 days of therapy with amoxicillin/clavulanate 500 mg/125 mg 3 times daily,<sup>62</sup> cefuroxime axetil 250 mg twice daily,<sup>63</sup> or a 10-day course of therapy with telithromycin 800 mg once daily.<sup>64</sup>

Five- and 10-day regimens of telithromycin were similarly effective for treatment of AS. Adults with clinical and radiological evidence of acute sinusitis of less than 1-month duration were randomized to telithromycin 800 mg once daily for 5 days (n = 170) or 10 days (n = 171). The results of the trial demonstrated equivalent clinical cure rates in the per-protocol population (91.1% vs 91.0%) for the 5- and 10-day dosing regimens. A satisfactory bacterial outcome was achieved in 92.9% (65/70) and 89.9% (62/69) of patients, respectively.<sup>64</sup>

Five days of telithromycin was found to be as effective as a 10-day course of therapy with cefuroxime axetil. Adults and adolescents with clinical and radiological evidence of AS of less than 28 days duration were randomized to telithromycin 800 mg once daily for 5 days (n = 260) or cefuroxime axetil 250 mg twice daily for 10 days (n = 125). Clinical cure rates were similar for telithromycin and cefuroxime axetil in the per-protocol population (85.2% vs 82.0%). A satisfactory bacterial outcome was observed in 84.0% (84/100) of telithromycin patients and 79.6% (39/49) of cefuroxime patients.<sup>63</sup>

Five days of telithromycin was also found to be as effective as a 10-day course of therapy with amoxicillin/clavulanic acid. Adults

with clinical and radiological evidence of AS of less than 28 days duration were randomized to telithromycin 800 mg once daily for 5 days (n = 201) or 10 days (n = 204) or amoxicillin/clavulanic acid 500 mg/125 mg 3 times daily for 10 days (n = 202). Clinical cure rates were similar for the 5-day and 10-day regimens of telithromycin (75.3% and 72.9%, respectively) and amoxicillin/clavulanic acid (74.5%) in the per-protocol population.<sup>62</sup>

In summary, 5 days of therapy with telithromycin 800 mg once daily was as effective as 10 days of therapy with once-daily telithromycin, twice-daily cefuroxime axetil, or 3-times-daily amoxicillin/clavulanic acid for the treatment of AS.

**Acute Exacerbations of Chronic Bronchitis.** The efficacy of telithromycin for the treatment of AEBCB has been studied in 3 trials with a total of 1249 patients. In these trials, telithromycin 800 mg once daily for 5 days was compared with 10 days of therapy of clarithromycin 500 mg twice daily,<sup>65</sup> amoxicillin/clavulanate 500 mg/125 mg 3 times daily,<sup>66</sup> and cefuroxime axetil 500 mg twice daily.<sup>67</sup> In these studies, a clinical diagnosis of AEBCB was based on Anthonisen criteria (increases in dyspnea, sputum production, and sputum purulence).<sup>75</sup>

Five days of telithromycin was found to be as effective as a 10-day course of therapy with cefuroxime axetil. Adults with clinical evidence of AEBCB were randomized to telithromycin 800 mg once daily for 5 days (n = 182) or cefuroxime axetil 500 mg twice daily for 10 days (n = 191). Clinical cure rates were similar for telithromycin and cefuroxime axetil in the per-protocol population (86.4% vs 83.1%). A satisfactory bacterial outcome was observed in 76.0% (19/25) of telithromycin patients and 78.6% (22/28) of cefuroxime patients.<sup>67</sup>

Five days of telithromycin was also found to be as effective as a 10-day course of therapy with amoxicillin/clavulanate. Adults with a history of chronic bronchitis or chronic obstructive pulmonary disease with bronchodilator response and clinical evidence of AEBCB were randomized to telithromycin 800 mg once daily for 5 days (n = 163) or amoxicillin/clavulanate 500

mg/125 mg 3 times daily for 10 days (n = 161). Clinical cure rates were similar for telithromycin and amoxicillin/clavulanate in the per-protocol population (86.1% vs 82.1%), and satisfactory bacterial outcome was observed in 69.2% (27/39) and 70.0% (21/30) of patients, respectively.<sup>66</sup>

Further, 5 days of telithromycin was found to be as effective as a 10-day course of therapy with clarithromycin. Adults with clinical evidence of AECB were randomized to telithromycin 800 mg once daily for 5 days (n = 270) or clarithromycin 500 mg twice daily for 10 days (n = 282). Clinical cure rates were similar for telithromycin and clarithromycin in the per-protocol population (85.8% vs 89.2%).<sup>65</sup>

In summary, 5 days of therapy with telithromycin 800 mg once daily was as effective as 10 days of therapy with twice-daily clarithromycin, twice-daily cefuroxime axetil, or 3-times-daily amoxicillin/clavulanic acid for the treatment of AECB. Concerns of a higher rate of reinfection with a 5-day course of therapy for AECB were unsubstantiated. In the head-to-head trial with the 10-day course of therapy with amoxicillin/clavulanate, the 5-day course of therapy with telithromycin resulted in fewer reinfections (1.3%; 2/160) than amoxicillin/clavulanate (5.7%; 9/160).<sup>66</sup>

**Community-acquired Pneumonia.** The efficacy of telithromycin for the treatment of CAP has been studied in 8 trials with a total of 1925 patients.<sup>59,68-74</sup> Of these 8 trials, 4 were double-blind, randomized trials comparing telithromycin 800 mg once daily for 7 to 10 days with 10 days of therapy with clarithromycin 500 mg twice daily,<sup>71,73</sup> 10 days of amoxicillin 1000 mg 3 times daily,<sup>70</sup> and 7 to 10 days of trovafloxacin 200 mg once daily.<sup>72</sup> In these studies, a diagnosis of CAP was based on clinical signs, symptoms, and radiological evidence of bacterial pneumonia.

Ten days of telithromycin was found to be as effective as a 10-day course of therapy with high-dose amoxicillin. Adults with acute CAP were randomized to 10 days of therapy with telithromycin 800 mg once daily (n = 199) or amoxicillin 1000 mg 3 times daily (n = 205). Clinical cure rates

were similar for telithromycin and amoxicillin in the per-protocol population (94.6% vs 90.1%), and satisfactory bacterial outcome was observed in 90% (36/40) and 87.5% (35/40) of patients, respectively.

Seven or 10 days of telithromycin was also found to be as effective as a 10-day course of therapy with clarithromycin in 2 studies.<sup>71,73,76</sup> Adults with CAP were randomized to telithromycin 800 mg once daily for 7 days (n = 195)<sup>76</sup> or 10 days (n = 204)<sup>71</sup> or clarithromycin 500 mg twice daily for 10 days (n = 187 and n = 212, respectively). Clinical cure rates were similar for telithromycin and clarithromycin in the per-protocol population (88.8% and 88.3% for 7 and 10 days of telithromycin vs 91.8% and 88.5% for 10 days of clarithromycin, respectively) in each trial. A satisfactory bacterial outcome was achieved in 80.0% and 89.3% of patients receiving 7 and 10 days of telithromycin, and 83.3% and 96.4% of clarithromycin patients in each trial.

Before the removal of trovafloxacin from the outpatient market because of safety concerns, a 7- to 10-day course of therapy with telithromycin was found to be as effective as a 7- to 10-day course of therapy with trovafloxacin for CAP. Adults with acute CAP were randomized to 7 to 10 days of therapy with telithromycin 800 mg once daily (n = 100) or trovafloxacin 200 mg once daily (n = 104). Clinical cure rates were similar for telithromycin and trovafloxacin in the per-protocol population (90.0% vs 94.2%). A satisfactory bacterial outcome was observed in 92.9% (13/14) of telithromycin patients and 100.0% (22/22) of trovafloxacin patients; this difference did not achieve statistical significance.<sup>72</sup>

In summary, telithromycin 800 mg once daily for 7 to 10 days was found to be as effective as 7 to 10 days of therapy with high-dose amoxicillin, clarithromycin, and trovafloxacin.

#### **Safety Data, Warnings, and Adverse Events**

Like macrolides, telithromycin has the potential to prolong the QT<sub>c</sub> interval of the electrocardiogram in some patients. QT<sub>c</sub> prolongation may lead to an increased risk for ventricular arrhythmias, including torsades

de pointes. Thus, telithromycin should be avoided in patients with congenital prolongation of the  $QT_c$  interval, and in patients with ongoing proarrhythmic conditions, such as uncorrected hypokalemia or hypomagnesemia, clinically significant bradycardia, and in patients receiving Class IA (eg, quinidine and procainamide) or Class III (eg, dofetilide) antiarrhythmic agents.<sup>19</sup> No cardiovascular morbidity or mortality attributable to  $QT_c$  prolongation occurred with telithromycin treatment in 4780 patients in clinical efficacy trials, including 204 patients having a prolonged  $QT_c$  at baseline.

Exacerbations of myasthenia gravis have been reported in patients with myasthenia gravis treated with telithromycin. This has sometimes occurred within a few hours after intake of the first dose of telithromycin. Reports have included life-threatening acute respiratory failure with a rapid onset in patients with myasthenia gravis treated for RTIs with telithromycin. Telithromycin is not recommended in patients with myasthenia gravis unless no other therapeutic alternatives are available. If other therapeutic alternatives are not available, patients with myasthenia gravis taking telithromycin must be closely monitored.<sup>19</sup>

The pooled safety and tolerability data from all telithromycin phase 3 clinical trials demonstrate that telithromycin 800 mg once daily for up to 10 days is a safe and well-tolerated agent for RTIs.<sup>59</sup> Most adverse events were transient and were mild to moderate in severity.

In the controlled phase 3 clinical trials, 49.9% (1348/2702) of patients receiving telithromycin experienced one or more treatment-emergent adverse events, compared with 48.4% (1035/2139) of patients receiving a comparator.<sup>59</sup> The most frequently reported adverse events in the clinical trials were gastrointestinal in nature; the most common treatment-related adverse events in patients receiving telithromycin or a comparator were diarrhea (10.8% vs 8.6%), nausea (7.9% vs 4.6%), headache (5.5% vs 5.8%), dizziness (3.7% vs 2.7%), and vomiting (2.9% vs 2.2%).<sup>59</sup> A similar number of patients discontinued therapy with telithromycin (4.4%) or the compar-

ator (4.3%) because of adverse events; gastrointestinal adverse events such as diarrhea, nausea, and vomiting were most likely to lead to therapy discontinuation.<sup>59</sup>

Hepatic adverse events were low and balanced between treatment groups (3.4% of telithromycin subjects, 3.2% of comparator subjects). Across all studies, elevations of alanine aminotransferase (ALT) >3 times the upper limit of normal occurred in 1.6% of telithromycin patients and 1.7% of comparator subjects.<sup>59</sup> Also, since macrolides are known to impact cardiac repolarization, the  $QT_c$  interval data for telithromycin was compared with that of clarithromycin. Telithromycin was comparable with clarithromycin in respect to  $QT_c$  interval changes; the frequency of subjects with  $QT_c$  increases  $\geq 60$  ms while receiving therapy was low and similar between treatment groups, as was the frequency of subjects with  $QT_c$  outliers. Further, no subject in either treatment group in clarithromycin-controlled studies had a  $QT_c$  value  $\geq 500$  ms.<sup>59</sup>

Telithromycin has also been associated with transient visual disturbances, including blurred vision, difficulty focusing, and diplopia.<sup>59</sup> Reported rates of blurred vision in phase 3 clinical trials were 1.1% for telithromycin and 0.3% for the comparator agents.<sup>19</sup> Overall, telithromycin was well tolerated among various high-risk patient groups, including severely ill patients, the elderly, and patients with renal and hepatic insufficiency.

A postmarketing observation study of the effectiveness and tolerability of telithromycin began in Germany in 2001.<sup>77</sup> An interim evaluation was performed in July 2002 based on data from more than 24 000 patients. A low incidence of mild-to-moderate adverse events (2.2%) was reported, led by adverse events affecting the gastrointestinal tract (1.5%), the central nervous system (0.5%), and the skin (0.2%).<sup>78</sup> Ocular disorders, such as blurred vision, were reported in 0.2% of patients.

### Conclusion

Despite increased awareness about the consequences of bacterial resistance,<sup>79</sup> resistance among the most prevalent CARTI

pathogens to penicillins and macrolides continues to increase,<sup>4,80-82</sup> threatening the utility of those antibiotic classes. Ketolides are a new class of antibiotics designed with specific attributes to overcome bacterial resistance mechanisms that now render some empiric therapies ineffective, and, in addition, have the potential to curb the growth of antimicrobial resistance.

Telithromycin is the first member of the ketolide class available in the United States. It possesses a tailored spectrum of activity against the typical and atypical causative pathogens for CARTIs, including MDRSP. Telithromycin exhibits a tailored spectrum of activity with pharmacokinetic and pharmacodynamic attributes (potency, half-life, bactericidal activity, and binding affinity at multiple sites) that result in bacterial eradication with a low potential for the development of resistant organisms. The efficacy of telithromycin for the treatment of AS, AECSB, and CAP has been demonstrated in numerous phase 3 clinical trials. The data confirm that telithromycin is as efficacious as penicillins, macrolides, cephalosporins, and fluoroquinolones. The safety of telithromycin has been demonstrated in clinical trials, with adverse events that were mild to moderate, transient in nature, and occurring at rates similar to empiric therapies.

When making formulary decisions, it is important to consider all of the properties and attributes of an agent, especially those within a new class. Critical questions that should be asked are: "Do these properties and attributes contribute to improving patient outcomes?" and "Do the ketolides offer economic advantages over empiric therapies in the treatment of CARTIs?" Dr Diana Brixner will help to answer these matters further in our next article.

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