Editorial

Ketolide antibiotics: will they ever be used for community-acquired pneumonia?

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There is no perfect antibiotic for community-acquired pneumonia (CAP). β-lactams do not cover atypical organisms, most importantly, *Legionella*. Fluoroquinolones remain active against *Streptococcus pneumoniae* and cover atypical bacteria, but are associated with serious side effects including tendon rupture and a variety of neurologic side effects. They may also increase the risk of *Clostridium difficile* colitis more than other antibiotics commonly used for CAP. Macrolide antibiotics are generally well tolerated, are active against atypical organisms and may improve outcomes via a non-antimicrobial immunomodulatory effect; however in most parts of the world, there is a high prevalence of macrolide resistant *Streptococcus pneumoniae*. In China, macrolide resistance is a significant issue for both S. *pneumoniae* and Mycoplasma *pneumoniae* (1,2). In addition, some macrolides have poor *in vitro* activity against organisms such as *Hemophilus influenzae* and methicillin sensitive *Staphylococcus aureus*.

Ketolide antibiotics, sometimes described as next-generation macrolides, were developed to address some of these concerns. The results of a large clinical trial studying the efficacy and safety of the ketolide antibiotic, solithromycin, were recently published in the journal, Clinical Infectious Diseases by File *et al.* (3). This commentary will review the history of ketolide development, as well as the clinical trial results and current status of solithromycin with respect to the treatment of community-acquired bacterial pneumonia (CABP).

Macrolide antibiotics inhibit bacterial protein synthesis by binding to the 50S ribosome of several strains of bacteria that are commonly implicated in community-acquired pneumonia, including (but not limited to) Gram positive cocci such as *Steptococcus* spp., some strains of *S. aureus*, *H. influenza*, *Moraxella catarrhalis* and the so-called atypical bacteria. Some of these bacteria may exhibit resistance to macrolide antibiotics through alterations of the ribosomal binding site (erm) or due to an efflux pump (mef) that removes the antibiotic from the bacteria. The ketolide antibiotics thwart the occurrence of resistance via the erm mechanism as their structure allows them to bind to two (telithromycin) or three (solithromycin) sites on the ribosome (4). Activity in the face of bacterial efflux pumps is more variable, with limited activity of telithromycin in the face of the mef mode of resistance, while solithromycin appears to retain its anti-microbial activity, possibly due to its enhanced binding to the ribosomal site in addition to its structure being less conducive to action by the efflux pump (4). In addition to their anti-microbial activity, evidence has accumulated that macrolide antibiotics possess potent immunomodulatory effects, and that these properties may be associated with improved outcomes in a wide variety of infectious and inflammatory conditions. Ketolide antibiotics appear to retain these immunomodulatory properties (5).

Telithromycin, the first ketolide developed, was approved

for use in the United States in 2004. However, shortly after its approval, there were reports of severe hepatotoxicity associated with telithromycin use and it was removed from the US market by the manufacturer after the Food and Drug Administration (FDA) markedly restricted the indications for its use and gave it a "black box" warning. Shortly thereafter, its use in Europe was similarly limited by the European Medicines Agency. Telithromycin was also associated with temporary adverse visual side effects and severe exacerbations of myasthenia gravis. Subsequent investigation suggests that these effects were due to binding of the drug to nicotinic anticholinergic receptors in nerves serving the affected organs (6). This binding appears to be mediated by a pyridine side chain present in telithromycin. This moiety is not possessed by either cethromycin or solithromycin, so if the proposed mechanism of these adverse events is correct, we should not expect these events to occur with these drugs.

Cethromycin was the next ketolide studied for use in CABP. However, it was denied approval by the FDA in 2009, after a conclusion that the drug was proven safe, but that insufficient evidence of efficacy was provided. With that bleak background, the next ketolide to be developed for use in CABP, was solithromycin.

Solithromycin appears to have many characteristics which would make it an ideal antibiotic for CAP. It demonstrates activity against common bacterial CAP pathogens such as *S. pneumoniae*, *H. influenzae*, *M. catarrhalis* and many methicillin sensitive *S. aureus* isolates (7). For most respiratory pathogens, it is more potent than azithromycin, however in one study it was less potent against *H. influenza*, while in another, it possessed approximately equivalent activity (7,8). It is highly active *in vitro* against macrolide resistant *S. pneumoniae* (9). In a study of 272 macrolide resistant isolates obtained from patients with CAP from across the United States, solithromycin inhibited the growth of all 272 isolates at a concentration of ≤0.5 µg/mL. Solithromycin also demonstrated superior *in vitro* activity against 196 isolates of L. pneumophila compared to azithromycin (10). The anti-inflammatory effects of macrolides may play an important role in their success in treating respiratory infections. Solithromycin appears to retain these effects. It inhibited a variety of monocyte inflammatory responses to lipopolysaccharide and reduced alveolar neutrophil accumulation in mice exposed to cigarette smoke (10).

Two clinical trials investigating the use of solithromycin for CABP had been performed prior to the Phase III trial recently published by File *et al.* in Clinical Infectious Diseases (3). A Phase II trial double-blind randomized controlled trial published in 2013 compared the outcomes of 132 patients with CAP randomized to either oral solithromycin (800 mg first dose, followed by 400 mg once a day for four additional days) or levofloxacin 750 mg a day for five days (11). Approximately 75% of the patients were pneumonia severity index (PSI) class 2, and approximately 20% were class 3. Most outcomes were similar, with clinical success at the test of cure visit 84.6% in the solithromycin group and 86.6% in the levofloxacin group. Treatment emergent adverse event were more common in the levofloxacin group, and antibiotic discontinuation due to adverse events occurred in 6 levofloxacin patients and no solithromycin patients. Importantly, there were no neurologic or visual adverse events reported in the solithromycin group. Minor liver chemistry abnormalities were seen in a few patients in both groups.

A larger study of solithromycin for CABP was published in 2016 (12). The same oral solithromycin regimen (426 patients) was compared to a 7 day course of oral moxifloxacin (434 patients). Patients were sicker than those in the Phase II study, with approximately 50% in each group being PSI class III or IV. The primary outcome was early clinical response. Solithromycin was non-inferior to moxifloxacin with respect to this outcome, achieved in 333 (78.2%) solithromycin patients and 338 (77.9%) patients in the moxifloxacin group [difference 0.29; 95% confidence interval (CI), –5.5 to 6.1]. Adverse events were similar in both groups. There was no signal for the visual adverse events or severe hepatotoxicity seen previously in association with telithromycin.

The second phase III study of solithromycin (SOLITAIRE-IV) was published in October, 2016 by File *et al.* in the journal Clinical Infectious Diseases (3). It was designed as a non-inferiority trial (10% margin) to evaluate the efficacy and safety of intravenous (IV)-to-oral solithromycin in comparison with IV-to-oral moxifloxacin in adult patients with CABP.

Patients had to have PSI score II–IV and were excluded if they had a recent hospitalization, residence in a nursing facility or immunosuppression. Patients were randomized 1:1 to receive either IV to oral solithromycin or moxifloxacin. The initial dose for each arm was intravenous and the switch to oral therapy was at the discretion of the investigator. The primary endpoint was early clinical response (ECR) at 72 hours of at least 2 of 4 cardinal symptoms (cough, dyspnea, chest pain, or purulent sputum)

among the intention to treat population.

The study included 863 patients from 22 countries representing all continents except Australia and Antarctica. The two patient groups were well matched, with a mean age of approximately 60 years of age. Approximately ½ of the patients in each group were in PSI class III, with approximately 30% in risk class IV. Pathogens were identified in approximately 40% of patients, and included the range of pathogens expected in CABP, including atypical agents. Approximately 50% of the pathogens detected in each group were S. *pneumoniae*. Among the S. *pneumoniae* isolates, approximately 25% were macrolide resistant and 25% were multi-drug resistant. A small number of patients in each treatment arm grew pathogens that solithromycin would not be expected to be active against, including enteric gram negative bacilli and non-fermenters such as Pseudomonas aeruginosa.

Solithromycin was non-inferior to moxifloxacin. Among the ITT population, 79.3% of solithromycin patients and 79.7% of moxifloxacin patients achieved ECR (difference, –0.46; 95% CI, –6.1 to 5.2). The two groups also had similar outcomes in the micro-ITT population and among only PSI class III and IV. Similarly, there were no significant differences in secondary outcomes including clinical success at the short-term follow up visit (day 12-17), achieved in 84.6% of solithromycin patients and 88.6% of moxifloxacin patients among the ITT population.

Solithromycin exhibited excellent *in vitro* activity to the most common pathogens detected, with MIC_{50}/MIC_{90} for S. *pneumoniae* of 0.008/0.06 μg/mL and, MIC_{50}/MIC_{90} for *Mycoplasma pneumoniae* of ≤0.000032/≤0.000032. Both of these were better than for moxifloxacin. For macrolide-resistant S. *pneumoniae*, the ECR rate for solithromycin was 83% (10/12 patients) and for moxifloxacin was 71% (10/14) patients. Among patients with bacteremia, 9 of 14 solithromycin recipients and 7 of 8 moxifloxacin recipients achieved ECR.

Of course, given the concern with ketolide safety, the incidence of adverse events was reported in detail. Overall, 223 solithromycin patients (51.6%) and 148 moxifloxacin patients (34.7%) experienced at least one treatment emergent adverse event (TEAE). The higher rate of adverse events among the solithromycin patients was due infusion-related events such as pain, phlebitis and erythema (31.3%) compared to only 5.4% of patients in the moxifloxacin arm. However, TEAEs leading to early study drug discontinuation were similar for both groups, 5.8% of solithromycin patients and 4.2% of moxifloxacin patients. Serious adverse events occurred at a similar rate in each group (6.9% solithromycin *vs.* 5.4% moxifloxacin). No patient had symptomatic increases in liver laboratory tests, but a higher percentage of patients in the solithromycin arm had an increase in alanine aminotransferase to >3 times the upper limit of normal (ULN) (9.1%) than among the moxifloxacin group (3.6%). Increases to 5 times the ULN were also more common in the solithromycin group (3.1 *vs.* 0.7%). There were no increases to >10 times the ULN. No patients in the solithromycin group had a visual adverse event.

Overall, the results suggest that solithromycin is an effective antibiotic for the treatment of CABP. While there were no cases of severe liver injury, mild increases in liver-related laboratory testing were commonly seen with solithromycin. Since the severe liver injury seen with telithromycin was a very rare occurrence, seen only after release of the drug, too few patients have been exposed to the solithromycin to prove on an empirical basis that it does not cause this complication. Nonetheless, the report suggesting that the specific structure of telithromycin may be responsible for the hepatic and visual adverse events was a reason for optimism with respect to the future of solithromycin. It is perhaps important to note the visual adverse events with telithromycin were common enough that they were seen during the Phase III studies, suggesting that solithromycin may indeed not cause these events and providing support for the proposed mechanism of these events.

In December, 2016, shortly after the publication of the Solitaire IV study (3), the United States FDA notified the manufacturer (Cempra Inc., USA) that it could not approve solithromycin for use without more data (13). The FDA did not mention any concerns regarding the efficacy for CABP, but determined that not enough patients had been exposed to the drug to rule out the risk of severe liver injury. The FDA specifically suggested that 9,000 patients would need to be exposed to adequately address that concern. Given the safety concerns with telithromycin, and the liver laboratory value elevations seen with solithromycin, this response is perhaps not very surprising. It appears that the FDA was not convinced by the proposed mechanism of liver injury (the pyridine moiety binding to nicotinic receptors) that would suggest that solithromycin would not cause severe liver injury.

On the face of it, ketolide antibiotics would appear to possess numerous characteristics that would make them a desirable choice for the monotherapy of CABP. The

available data with solithromycin demonstrate that they are non-inferior to fluoroquinolones with respect to efficacy. Furthermore, the data to-date suggest that clinically significant adverse event rates are similar compared to fluoroquinolones, although only 920 patients have been exposed to therapeutic courses of solithromycin. If proven safe from the standpoint of liver toxicity, solithromycin would appear to represent a promising agent for the treatment of CABP. However, at this time, there has been no indication from the manufacturer as to whether or not it will proceed with further studies, as requested by the FDA. Clinicians who treat CABP can only wait to see what the future brings.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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