



Solithromycin for community acquired pneumonia in adults

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Community-acquired pneumonia (CAP) is an immense public health problem owing to its morbidity, economic burden on the society, long term effects on the quality of life, and mortality. With almost 3.5 million deaths yearly, it is one of the leading causes of death worldwide (1). Both the incidence and complication rates for CAP are greater at the extremes of age, with the overall rate in adults ranging from 5–11 cases per 1,000 persons/year, but increasing to 20 per 1,000 among those above 60 with an overall mortality rate of 8–15% (2,3).

A number of pathogens are known to cause CAP; most important among them are bacteria such as *Streptococcus pneumoniae* and *Haemophilus influenzae* followed by atypical organisms, namely Mycoplasma, Chlamydia and Legionella. *Staphylococcus aureus*, gram-negative bacilli and anaerobes are important causative agents in some populations (4). The selection of an antimicrobial agent for empirical therapy in Community acquired bacterial pneumonia (CABP) is based on a number of factors. They can be related to the pathogen, e.g., the most likely causative organisms, local antimicrobial susceptibility pattern of bacterial agents; patient related, e.g. risk group stratification of the patient, allergy, intolerance; and drug related factors, e.g. pharmacokinetics, pharmacodynamics, previous use, likely compliance, cost, potential for adverse effects and drug interactions (4-6).

Increasing resistance to the commonly used antimicrobials for CABP such as β -lactams and macrolides is observed amongst the causative pathogens (4). The

SENTRY program collecting pneumococcal isolates across the US reported a striking increase in the resistance rate to β -lactams between 2004 and 2009. The sensitivity rates decreased from 94.7% to 84.1% for penicillin and 97.4% to 87.5% for ceftriaxone. Macrolide susceptibility rates too fell from 82.2% to 60.8% (7). Resistance rates of >20% was also observed in the European surveillance program (8). AWARE program reported a resistance rate of 26.3% to ampicillin in *H. influenzae* (9). Prevalence of macrolide resistant *M. pneumoniae* was found to be >40% in Japan, 80–90% in China, and 3–10% in Europe and the US (10). Failure of macrolide treatment in CABP is a leading cause of hospitalization and death in adults in US (11) and this is probably secondary to macrolide resistance (12). In this context, the lack of new antibiotics is a major cause for concern (4).

Current guidelines (5) recommend treatment of CABP in adults with a fluoroquinolone or a beta-lactam plus a macrolide. But association of fluoroquinolone with significant adverse events prompted the FDA to update the US labeling and medication guides for all fluoroquinolones (13). There is also an increasing realization that fluoroquinolones should be preserved for use in hospitalized critically ill patients where they may be life-saving (14). Therefore, an increasing need was felt to find an antibiotic with both parenteral and enteral preparation that can be safely and effectively used as a monotherapy in moderate to severe cases of CABP in adults.

Solithromycin, a fourth generation macrolide, is the first fluoroketolide with activity against most of the frequently

isolated bacteria in CAP, including atypical bacteria as well as macrolide-resistant *Streptococcus pneumoniae* (15). A double-blind, randomized, multicenter phase II study enrolling 132 adult CABP patients with pneumonia severity index (PSI) classes II–IV evaluated oral solithromycin in comparison to oral levofloxacin (16). In the intention-to-treat population, clinical success was observed in 84.6% patients receiving solithromycin and 86.6% on levofloxacin. Oral solithromycin also showed efficacy comparable to that of levofloxacin in the treatment of CABP in other subgroup analyses as well. The SOLITAIRE-ORAL study (17), which was a double-blind, randomized, non-inferiority phase III trial, compared once daily (OD) oral solithromycin with OD oral moxifloxacin. There were total 860 patients with a PSI risk class of II–IV. In the intention-to-treat analysis solithromycin was found to be non-inferior to moxifloxacin. Although some pneumococcal isolates were macrolide resistant but solithromycin sensitive, in view of the small number of such cases, it was not possible to show solithromycin efficacy in these strains.

The recent SOLITAIRE-IV study (18) which evaluated the efficacy and safety of intravenous to oral solithromycin compared to intravenous to oral moxifloxacin in the treatment of patients with CABP recruited a total of 863 patients belonging to the Pneumonia Outcomes Research Team (PORT) class II–IV from 147 centers in 22 countries across North America, Latin America, Europe and Asia. In this study (PSI score 51 to 130 (PORT II capped at 25%; and $\geq 25\%$ PORT IV) the investigators had chosen to include patients with a overall greater CABP severity at enrollment compared to the SOLITAIRE-ORAL study (PSI score 51–105 with PORT II capped at 50%) (17), as more severe cases are expected to require initial IV therapy. Randomization was stratified by geographic region, history of asthma and/or chronic obstructive pulmonary disease (COPD), and PORT II *vs.* III/IV. Patients in both treatment groups were administered IV treatment on day 1 and from day 2, were transitioned to oral therapy at the investigator's discretion if they met clinical improvement criteria. Patients in the solithromycin group received an IV treatment regimen of 400 mg OD and for transition to oral solithromycin, the first oral dose was 800 mg single dose, followed by 400 mg OD till day 7. For moxifloxacin both the oral and IV doses were 400 mg OD. Efficacy analyses was conducted at 72 hours after the first dose of study drug (day 4 visit) and for assessment of the primary outcome of early clinical response (ECR), at the end of treatment (EOT) visit, and at the short-term follow-up (SFU) visit

5 to 10 days after last dose of study drug. In addition, all-cause mortality was assessed through the late follow-up (LFU) visit 28 to 35 days after the first dose of study drug. Solithromycin was shown to be non-inferior to moxifloxacin for ECR with response rate in solithromycin and moxifloxacin groups being 79.3% and 79.7% respectively; the lower bound of the 95% CI for the treatment difference -6.1% , meeting the 10% non-inferiority margin. Similarly, non-inferiority of solithromycin was also demonstrated in the microbiologically confirmed cases and in subgroup analysis according to sex, age, history of asthma/COPD, prior antibiotic use, PORT risk class, and baseline symptoms of CABP. Clinical success at SFU was also comparable between the two treatment groups. Median duration of IV treatment and oral treatment was identical in both treatment groups and similar percentages of patients remained on IV therapy for 7 days (22.0% solithromycin *vs.* 25.6% moxifloxacin). Interestingly, 10.6% and 8.9% in the solithromycin and moxifloxacin groups prematurely discontinued study drug. This was mostly attributable to the higher rate of discontinuations due to infusion-related adverse events in the solithromycin group (2.3% with solithromycin, 0.2% with moxifloxacin), whereas, other adverse events were comparable between treatment groups.

The limitation of the SOLITAIRE-IV trial (18) was its short follow up. Patients were only followed up for 30 days, which did not allow for analysis of the effects of antibiotics on long-term mortality. This is important because clarithromycin has been associated with increased cardiovascular events at one year in the setting of acute exacerbations of COPD or CAP (19).

Though the efficacy of solithromycin for CABP in adults has been well established, unfortunately, it is the concern regarding safety that is still in doubt. Macrolides have been associated with QT prolongation and risk for torsades de pointes. In contrast, solithromycin was found in a thorough QT study even at a suprathreshold exposure (20). Though solithromycin has been shown to be safe even in patients with moderate to severe hepatic impairment (21), the FDA did not approve its use due to fear of hepatotoxicity (22). They recommend new safety study to further characterize the liver toxicity. It would be required to treat nearly 9,000 patients with solithromycin to effectively examine the probability of serious drug-induced liver injury! This is related to the previous experience with telithromycin, the first ketolide, which despite having a low occurrence of hepatic events in the initial NDA safety database of almost 3,400 patients, during the post-market phase was marked by the occurrence

of severe hepatotoxicity resulting in deaths and a liver transplantation (23).

In conclusion, solithromycin is an exciting new macrolide antibiotic with broad range of activity against the usual pathogens causing CABP in adults, having an OD dosing and available in both IV and oral formulations. Notwithstanding the safety concerns, provided it receives marketing approval, it is expected to give more flexibility in the management of adult CABP patients as it allows patients to be switched from IV to oral drug with efficacy akin to other commonly used macrolides without any significantly increased risk of treatment related adverse events.

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Footnote

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

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