

Solithromycin: A New Ketolide Antibacterial Agent in Clinical Trials

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Abstract

Solithromycin is a novel agent of macrolide antimicrobial classes that demonstrates treatment option in community-acquired pneumonia (CAP). It showed bactericidal effect against major respiratory tract pathogens namely, *Streptococcus pneumoniae*, *Staphylococcus aureus* and *Haemophilus influenzae* even against strains exhibiting resistance to commonly used antibiotics. Solithromycin demonstrates broad-spectrum antibacterial activity together with other features like intracellular accumulation and anti-inflammatory effect. It showed moderately severe adverse events during clinical trials and demonstrated favourable tissue penetration and pharmacokinetic properties. Solithromycin showed non-inferiority to moxifloxacin in clinical trial indicating its possible treatment option in CAP and other lower respiratory tract infections in the future. This commentary describes recent advances regarding solithromycin that has been introduced into clinical trials.

Solithromycin (CEM-101) is a fourth-generation macrolide and belongs to fluoro ketolide agents. It demonstrated bactericidal activity during *in vitro* and *in vivo* studies against major respiratory tract bacterial pathogens including macrolide and penicillin resistant *Streptococcus pneumoniae* [1,2].

Solithromycin compared to other macrolides (e.g. clarithromycin), lacks L-cladinose in position C3 of the erythronolide ring that leads to a hydroxyl group oxidized to a keto group. This modification enhances acid stability and antimicrobial potency against macrolide-resistant isolates too [3-6]. Solithromycin differs from telithromycin due to a fluorine at position C2. When bound to the ribosome, this fluorine appears in close to the glycosidic bond (N-1) of C2611 of 23S rRNA, contributing to drug binding on the target and enhancing the agent's antibacterial activity. Thus, solithromycin is capable to bind to three different sites on the ribosome, by contrast, telithromycin binds only to two sites. This feature improves the activity of solithromycin in growth inhibition of *Streptococci* carrying the *erm* methyltransferase compared with macrolides lacking the C2 fluorine, indicating solithromycin's activity against macrolide-resistant isolates too [1,5,7]. Chemical structure characteristics of solithromycin include lack of pyridine moiety in its side chain that has been shown to be associated with nicotinic acetylcholine receptor inhibition, which is potentially the cause of certain adverse events (e.g. blurry vision, exacerbation of myasthenia gravis, and hepatotoxicity) [8,9]. The main antibacterial effect of solithromycin is the inhibition of 50S ribosomal unit formation thus it inhibits bacterial protein synthesis [5,10]. This antibacterial activity was detected in vitro *S. pneumoniae*, methicillin-susceptible and methicillin-resistant *Staphylococcus aureus* and *Haemophilus influenzae* [11]. Solithromycin achieves remarkable intracellular accumulation compared to currently available macrolides [12], this contributes to treat lower respiratory tract infections (LRTIs) of both extra- and intracellular pathogens [13]. Solithromycin demonstrates anti-inflammatory effect that can also be beneficial during treatment of LRTIs [14,15].

Pharmacokinetic investigations in human individuals during intravenous administration demonstrate approximately 67% bioavailability following orally administered solithromycin [1]. Food consumption did not interfere the bioavailability of solithromycin as peak plasma concentration (C_{max}), time to reach maximum plasma concentration (T_{max}), and area under the concentration time curve (AUC) following a single 400-mg dose in fasted (for at least 10 h) and fed (following a high-fat meal) conditions stayed at similar level [16]. A 542 L distribution volume of solithromycin was achieved

during a multiple-dose regimen of 800 mg followed by 400 mg daily for 4 days in healthy adults [17]. A high plasma protein binding (81%) features solithromycin [13]. The major metabolic pathway of solithromycin is through cytochrome P450, 3A4, with the most metabolites are involved in biliary excretion [17]. In a single-dose escalation study, half-life of solithromycin increased from 3 h with doses of 100 mg to 7 h with doses of 1600 mg. Generally, there were nonlinear increases in C_{max} and AUC $_{0-\infty}$ and a prolongation of T_{max} from 1.5 to 6 h over the range of doses [16]. In tissue distribution, solithromycin showed significant accumulation in alveolar macrophages compared with plasma, with a mean macrophage to plasma concentration ratio of 245 (range 44–515) [13].

Altogether two Phase II and two Phase III clinical trials have been conducted with solithromycin. A Phase II trial has evaluated safety and efficacy of solithromycin treatment in community-acquired bacterial pneumonia (Clinical Trials.gov registration number: NCT01168713). Another Phase II clinical trial was investigating solithromycin treatment in urogenital gonorrhea infection (Clinical Trials.gov registration number: NCT01591447).

A Phase III clinical trial demonstrated antibacterial efficacy and safety of oral solithromycin (800 mg on day 1 followed by 400 mg daily on days 2–5 and then placebo daily on days 6–7) versus oral moxifloxacin (400 mg daily for 7 days) for the treatment of community-acquired bacterial pneumonia in a global, double-blind, double-dummy, randomized, active-controlled, non-inferiority trial (SOLITAIRE-ORAL) (Clinical Trials.gov registration number: NCT01756339). During this study, a total of 860 patients were randomly assigned, with 426 receiving solithromycin and 434 receiving moxifloxacin. Baseline pathogens were identified from blood, respiratory samples whereas *S. pneumoniae* (23% of total patients), *H. influenzae* (16%), and causative agents of a typical pneumonia (24%). Successful baseline pathogen identification was in 55% of patients receiving solithromycin and in 52% of patients receiving moxifloxacin. The primary outcome was early clinical response, as defined by improvement in at least two of

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four symptoms (cough, chest pain, sputum production, and dyspnea) with no worsening in any symptom at 72 h after the first dose. Solithromycin was noninferior to moxifloxacin, with early clinical response in 78.2% versus 77.9% of patients receiving moxifloxacin (95% confidence interval [CI], 5.5 to 6.1). Treatment failure at short-term follow-up, which occurred 5–10 days following the end of treatment, occurred in 12% of patients receiving solithromycin and 9% of patients receiving moxifloxacin. This included lack of resolution, worsening of baseline or development of new symptoms, and the need for new antibacterial treatment [18].

In another Phase III trial (ClinicalTrials.gov registration number: NCT01968733) SOLITAIRE-IV, the efficacy and safety of intravenous-to-oral solithromycin were assessed against intravenous-to-oral moxifloxacin for the treatment of community-acquired bacterial pneumonia. In this randomized, global, double-blind, active-controlled, non-inferiority trial, all patients began treatment with 400 mg intravenous solithromycin or moxifloxacin, with a switch to the oral form of the medication (800 mg and then 400 mg daily for solithromycin; 400 mg daily for moxifloxacin) when clinically indicated for a total treatment duration of 7 days. The criteria for switching to oral therapy were improved signs and symptoms versus baseline, with patients being afebrile with a respiratory rate ≤ 24 breaths per minute, systolic blood pressure ≥ 90 mmHg, and O_2 saturation $\geq 90\%$ on room air. Patients had to have experienced an acute onset or worsening of three of four cardinal symptoms such as cough, dyspnea, chest pain, or purulent sputum production – plus one of the following: fever, hypothermia, and/or pulmonary consolidation. *S. pneumoniae* was the most common pathogen, accounting for more than 45% of baseline pathogens, followed by *Mycoplasma pneumoniae* over 19% with *H. influenzae*, *Legionella spp.*, and *S. aureus* each accounting for $\geq 10\%$. The primary end point was early clinical response (defined by improvement at 72 h after the first dose in at least two of the four cardinal symptoms, with no other antimicrobial agents received). Solithromycin demonstrated non-inferiority to moxifloxacin (79.3% of patients who received solithromycin showed early clinical response versus 79.7% of patients who received moxifloxacin [95% CI –6.1 to 5.2]). In both treatment arms, there was a median of 3-day duration of intravenous treatment and 4 days of oral treatment [19].

Adverse events of solithromycin were tested during Phase II and Phase III clinical trials, and solithromycin was well tolerated as usually mild adverse events appeared. The most frequent events were nausea, vomiting, diarrhea, transaminase elevation, headache, dizziness, insomnia, hypokalemia, hyponatremia, urticaria, and bilirubin elevation. During intravenous administration, a phlebitis, erythema, paresthesia, and thrombosis appeared. On the 4th of November 2016, the FDA has released a document regarding hepatotoxic adverse events during clinical trials of solithromycin. The rates of liver enzymes (alanine aminotransferase [ALT] and aspartate aminotransferase) were higher in solithromycin-treated patients than those of treated with moxifloxacin. These transaminase elevations remained asymptomatic without bilirubin elevation; however, the severe adverse events that occurred with telithromycin (e.g. hepatotoxicity) have not been detected. It has been also assumed that hepatotoxicity due to solithromycin therapy has not yet been adequately characterized (FDA) [4].

Competing Interests

The authors declare that there is no competing interest.

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