The pipeline of new antibiotics in community-acquired infection has been scarce in the last decades. Community-acquired pneumonia (CAP) remains as one of the main causes of mortality in the world and is responsible for many exacerbations of several comorbid conditions (1). Among the modifiable factors with a positive impact on CAP survival are those dependent on physician decisions, such as severity assessment and adequateness of prompt antibiotic treatment. Causative microorganisms in CAP, that is, excluding immunosuppressed patients and/or nosocomial infections, most frequently found are Streptococcus pneumoniae, Haemophilus influenzae, Legionella, Mycoplasma, and less often Staphylococcus aureus and Enterobacteriaceae (2). Among them, S pneumoniae is the most common CAP microorganisms worldwide and in the different clinical settings: ambulatory, hospital and in the intensive care unit. Moreover, S pneumoniae is the main causative microorganism in CAP episodes developing sepsis (3) and an initial adequate treatment was related to higher survival. When considering the elderly patient and those with comorbid conditions, S pneumoniae remains as the main microorganism in the immunocompetent host (4).

The current guidelines for the management of CAP consider the use of macrolide (MCL) in combination with beta-lactams in hospitalized patients and even in the outpatient if there are risk factors for resistance in S pneumoniae (5,6). The recommendations of USA guidelines point out that monotherapy with MCL is not adequate if there is a high level of resistance because they do not provide enough coverage. In fact, the increase of drug resistance is a global health concern with the potential negative consequence for the patients if prescribing inactive antibiotics against microorganisms. That circumstance makes the clinicians face two important issues: first, clearly identifying the etiology of multi-drug resistant (MDR) pathogens in community to avoid inadequate treatment and, second, to avoid overtreatment that eventually would contribute to increase subsequent resistance. This makes necessary to continuously monitor the evolution of MDR pathogens in clinical samples to know the current burden of resistance and increase awareness in physicians. In the literature, some authors proposed different scores to rule out resistance in order to provide help in the decision making process (7,8). Concerning CAP, resistance of S pneumoniae has been an important issue in the last decades. Although it has variations depending on the country and the patient risk factors, it is accepted that the percentage of MCL-resistant strains is rather high (12–21%), despite the fact that resistance against beta-lactams has decreased and is low against respiratory fluoroquinolones. Pneumococcal resistance is defined by the minimum inhibitory concentration (MIC) breakpoints that are determined by the Clinical and Laboratory Standards Institute (CLSI) and the European Committee on Antimicrobial Susceptibility Testing (EUCAST). The MIC breakpoints considered appropriate for penicillin in CAP are ≤2 mg/L for susceptible strains, 4 mg/L for intermediate strains, and ≥8 mg/L for resistant strains (9).

In Gram-positive cocci there are two main mechanisms of resistance to MCL: they include mef (macrolide efflux),
which represents lower levels of resistance, and erm (erythromycin ribosomal methylation), which is associated with higher resistance levels, while other mechanisms of resistance are less common, including mutations in ribosomal proteins or RNA (4). The presence of both resistance mechanisms is also appearing. The possibility of an escalation in MCL-resistance, very high and with strains of higher resistant level, is a concern because of the risk of treatment failure and it precludes or highly restricts the use of MCL in monotherapy. Nevertheless, Cilloniz et al. (10) found no evidence suggesting that patients hospitalized for macrolide-resistant S. pneumoniae pneumonia were more severely ill on presentation or had worse clinical outcomes if they were treated with guideline-compliant versus noncompliant regimens.

Solithromycin is a new macrolide, fluoroketolide, that has activity against the most frequent pathogens in CAP—typicals and atypicals—and more importantly against MCL-resistant bacteria (S pneumoniae and Mycoplasma) (11). It has been evaluated in two phase III trials and is undergoing regulatory review at the FDA. Solithromycin has the advantage of offering both oral and intravenous formulations. The current studied dosages were 400 mg infusion q24 hours with switching to 800 mg oral first dose, followed by 400 mg every 24 hours versus 400 mg q24 hours of moxifloxacin (12). In the study SOLITAIRE-IV, patients received identical oral dosing (13). The pharmacodynamics of solithromycin is best described by the ratio AUC0-24/MIC ratio. Its ability to concentrate in epithelial lung fluid and alveolar macrophages may contribute to its efficacy in treating CAP (11).

The study published by File et al.—SOLITAIRE-IV—aimed to evaluate the efficacy and safety of iv-oral solithromycin versus iv-oral moxifloxacin for CAP treatment (12). The study included a big population (863 patients) with different scores in PORT II-IV, randomized 1:1 to receive solithromycin or moxifloxacin for seven days. Among the exclusion criteria was a prolonged QT. Switch therapy was allowed after the first intravenous dose when clinically indicated. The main objective was to demonstrate no inferiority at early clinical response assessed at three days in an intention-to-treat (ITT) evaluation. The clinically evaluable (i.e., per-protocol) population was the subset of patients in the intention-to-treat population that were adherent to key protocol, inclusion and exclusion criteria, and procedures.

The baseline characteristics of patients in both arms showed similar characteristics of age, demographics, respiratory comorbid conditions and PORT risk classes and CURB scores. Concerning identified pathogens, the proportion of unknown etiology and causative microorganisms was similar although with a smaller percentage of bacteraemia in moxifloxacin arm and slightly higher MCL-resistance. The median duration of intravenous antibiotic treatment was the same in the two arms, and drug discontinuation occurred in 5.8% in the solithromycin arm and 4.2% in the moxifloxacin arm. The primary endpoint improvement at 72 hours after the first dose in at least 2 of 4 symptoms was similar in the ITT evaluation, 79.3% vs. 79.7% in the comparator arm, and 84 vs. 86% in the evaluable population. Non-inferiority is demonstrated in the subgroup of patients with PORT III-IV, although the group was small and the allowed margin for noninferiority was wider, 15%. Noninferiority was also found in the subset of patients with microbiologic identification in the ITT analysis. It is worth highlighting that there were fewer patients with bacteraemia in the solithromycin arm whereas there were more MCL-resistant pathogens in the moxifloxacin arm. Mortality was comparable in both arms.

In the SOLITAIRE-ORAL trial (13), the efficacy of oral solithromycin during five days (dosage 800 day 1 followed by 400 mg) vs. oral levofloxacin (750 mg) during seven days was investigated in a randomized study (1:1). Outcome rates evaluated by test-of-cure at days 4–11 days were 84.6% for solithromycin vs. 86.6% for levofloxacin in the ITT analysis. Gastrointestinal adverse events were more frequent for levofloxacin and there was also a favorable safety profile for solithromycin.

An additional and important effect of macrolides is their anti-inflammatory effect. Solithromycin also possesses a potent anti-inflammatory effect, which might be beneficial in treatment of CAP (14).

With regard to the safety profile of solithromycin, studies by of File et al. (12) and others (13) confirm a similar percentage of adverse events except for more frequent infusion site events, a well-known class effect of MCL. Also a more frequent increase in hepatic enzymes ALT and AST was reported, with a peak in day 4 and reduction at day 7. An important concern is the potential effect on QT prolongation. Darpo et al. (15) designed a thorough QT study with a three-way crossover design performed in healthy male and female subjects to evaluate the ECG effects of solithromycin. Forty-eight subjects were randomized to receive 800 mg of intravenous (iv) solithromycin, 400 mg of oral moxifloxacin and placebo in
three separate treatment periods. Continuous 12 lead ECGs were recorded at a pre-dose baseline and serially after drug administration for 24h. Solithromycin was well tolerated and effective in clinical trials (16).

In conclusion, recent randomized controlled phase II/III trials in mild-to-moderate CAP patients have demonstrated similar efficacy of oral and intravenous solithromycin compared to fluoroquinolones, with comparable systemic adverse events. However, studies of larger populations, more adequate to identify heart and infrequent adverse events, should be performed (17). We also need more clinical efficacy studies mainly in hospitalized CAP and/or bacteriemic episodes. There are reasons for optimism and we welcome a new antibiotic for CAP, although more data are necessary to completely establish its place in CAP, mainly if we are considering it for monotherapy.

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None

Footnote

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References


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