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REVIEW

## The role of solithromycin in the management of bacterial community-acquired pneumonia

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### ABSTRACT

The fluoroketolide solithromycin is 2-fold more potent *in vitro* than telithromycin against pneumococci (including macrolide-resistant strains) and *Haemophilus influenzae* and very active on pathogens causing atypical pneumonia. In contrast, it is a 30-fold less potent inhibitor of nicotinic receptors incriminated in telithromycin toxicity. In Phase II/III trials, oral solithromycin once-daily (800 mg on day 1; 400 mg on days 2–5) proved effective and safe when compared to respiratory fluoroquinolones for the treatment of community-acquired bacterial pneumonia (CABP). A Phase III intravenous trial vs. moxifloxacin has been recently completed for the same indication. Solithromycin may restore interest in ketolides as a first-line therapy for CABP. Solithromycin safety should nevertheless be confirmed in larger populations allowing for detection of rare adverse events.

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solithromycin; ketolide; community-acquired bacterial pneumonia; *Streptococcus pneumoniae*; *Chlamydomydia pneumoniae*; *Legionella pneumophila*; *Mycoplasma pneumoniae*; *Haemophilus influenzae*; moxifloxacin; levofloxacin

This review focuses on the possible role of the fluoroketolide solithromycin in the treatment of community-acquired bacterial pneumonia (CABP). It is primarily focused on pneumonia caused by bacterial agents, hence the acronym CABP used since a few years in the United States. Most European papers simply use the acronym CAP because many cases of pneumonia are of undetermined origin. However, it must be clear to the reader that solithromycin should only be used when there are clear indications or compelling suggestions that the pneumonia is of bacterial origin. After a global survey of the importance of this pathology in humans, we present the positioning of macrolides in its treatment, discuss the advantages of solithromycin over conventional macrolides and other ketolides, and summarize its current clinical development. We lastly present our personal opinion on the future of this molecule in this indication.

### Community-acquired bacterial pneumonia (CABP): epidemiology, etiology, and treatment

#### Epidemiology

Pneumonia remains one of the most severe diseases among community-acquired infections. It is associated with a high risk of morbidity and mortality, and represented the second cause of death worldwide in 2013, after ischemic heart disease and stroke [1]. Its incidence

ranges between 1.5 and 14 cases per 1000 person-years, with high variability between regions of the world [2] as well as between age groups. In children, CABP incidence reaches 36–40 cases per 1000 persons-years below the age of 5 years while decreasing to 11–16 per 1000 persons-years in older children. However, it still represents the first cause of infantile mortality in developing countries (see for review [3]). In adults, the incidence dramatically increases with age, ranging from 18.2 cases per 1000 person-years in the 65–69 year-age group to 52.3 per 1000 person-years in people over 85 years [4]. Risk factors for developing CABP are multifactorial [5]. They include environmental factors (air pollution, poor socioeconomical status, and contact with children), unhealthy habits (smoking and alcohol abuse), comorbidities (chronic respiratory diseases, obstructive sleep apnea, dysphagia, previous pneumonia, viral respiratory infection, HIV infection, immunosuppression, chronic liver, heart or renal disease, and neurological diseases), use of medications (proton pump inhibitors, benzodiazepines, and inhaled corticosteroids), or patient's status (age [low or high], malnutrition, dental care, and genetic predisposition).

The short-term mortality of pneumonia varies between 1% and 48% based on European statistics [6]. Associated risk factors related to the patient include male gender, bacteremia, multilobar infiltrate, pleuritic chest pain, neoplastic disease, leucopenia, hypothermia,

systolic hypotension, tachypnea, diabetes mellitus, and neurological diseases [2]. Moreover, recent exposure to the healthcare system, previous infection, and/or recent antibiotic treatment increase the risk of infections by multidrug-resistant pathogens and hence the risk of treatment failure [5,7]. Patients with an episode of CABP have a decreased long-term survival that can be as high as 50% after 5 years [8], the most frequent causes of death being malignancy, chronic obstructive pulmonary disease (COPD), and cardiovascular diseases [2].

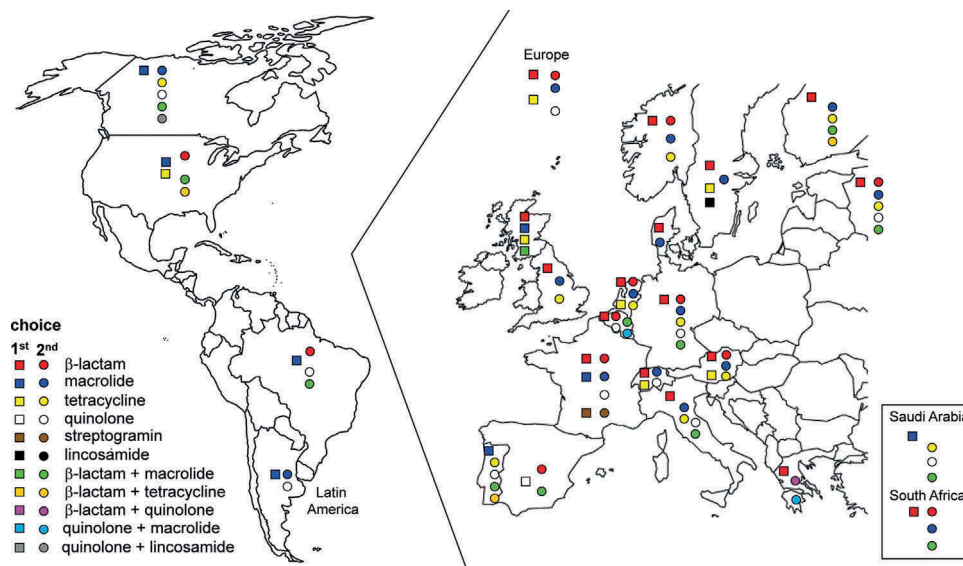
## Etiology

Etiology of CAP is highly variable across studies [9]. Moreover, no bacterial pathogen is isolated in about half of the cases [6]. Nevertheless, *Streptococcus pneumoniae* remains from far the most prevalent organism reported in most surveys and settings (outpatients, patients from nursing homes, and inpatients including those treated in the intensive care unit), accounting for 19–35% of cases [6,10–12]. *Chlamydia* species, *Chlamydophila pneumoniae*, *Mycoplasma pneumoniae*, *Haemophilus influenzae*, and viruses are each incriminated in 5–11% of the cases (with higher prevalence in elderly patients for *H. influenzae* [2.9–29.4%] and respiratory viruses [7.8–18.6%]), while Gram-negative enteric bacilli, *Legionella pneumophila*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Chlamydophila psittaci*, *Coxiella burnetii*, and *Moraxella catarrhalis* are usually less prevalent [2,9]. Yet, the etiology of CABP may also highly vary according to geographic areas,

with Gram-negative pathogens being more frequent in Asian surveys [13]. Specific risk factors have also been described for infections by penicillin- and multi-drug-resistant pneumococci (age >65 years,  $\beta$ -lactam therapy within the past 3 months, alcoholism, immunosuppression, multiple comorbidities, and exposure to a child in a day care center), enteric Gram-negative bacteria (residence in a nursing home, underlying cardiopulmonary disease, multiple comorbidities, and recent antibiotic therapy), or *P. aeruginosa* (bronchiectasis, corticosteroid therapy, and broad-spectrum antibiotic therapy for more than 7 days in the past month) [14].

## Current treatment

Treatment guidelines for CABP have been set up by scientific societies or national authorities in order to rationalize the selection of empirical antibiotherapy according to the severity of the infection and taking into account the most likely pathogens, individual risk factors, comorbidities, allergies, drug availabilities, and cost-effectiveness (see the general comments about guidelines in [5,15]). Figure 1, however, illustrates how variable these recommendations are, taking treatment options proposed for outpatients as an example, and this, even between regions with similar epidemiology an level of development. Thus, comparing the guidelines proposed in 2007 by the Infections Diseases Society of America/American Thoracic Society (IDSA/ATS) [16] and in 2011 by the European Respiratory Society (ERS) [17],



**Figure 1.** Pictorial representation of the diversity of guidelines for outpatients with CABP in Europe, North and Latin America and in 2 selected countries in Middle-East and Africa. Square symbols represent first line therapy and round symbols, alternative treatment options. (adapted and updated from [81]).

we see that the former recommend using macrolides as a first choice and doxycycline as an alternative for nonsevere disease in outpatients with no risk factors, while the latter favors amoxicillin or tetracycline and put macrolides as an alternative. In all other situations, IDSA/ATS recommends a combination of a  $\beta$ -lactam and a macrolide or, alternatively, a monotherapy with a respiratory fluoroquinolone (combined with a  $\beta$ -lactam for severe disease in patients hospitalized in ICU) while ERS rather recommends a respiratory fluoroquinolone in at-risk ambulatory patients, an aminopenicillin (in combination with a macrolide) or a respiratory fluoroquinolone in inpatients with moderate disease, and a third-generation cephalosporin plus a macrolide or a respiratory fluoroquinolone combined or not with a third-generation cephalosporin in ICU patients with severe symptoms.

Beside inconsistencies among guidelines, their lack of recent update is also problematic, most of them having been released before 2010. Rare recent updates have been published, most with no major changes from previous versions. A typical example is for the British Thoracic Society for which the lack of change in their 2015 guidelines over previous ones was justified by their 'coherence and consistency' as well as by a relative lack of substantial innovation in the field of CABP treatment [18]. We do not share this point of view and rather urge competent authorities to review all these guidelines and, if possible, make them more homogenous for groups of countries and/or regions where epidemiology and drug availabilities are similar. Updating guidelines over current ones should also take into account the changes of susceptibility profile of the main offending organisms over time as well as the approval of new antibacterial agents such as ceftaroline [19] and ceftobiprole [20] (originally designed for displaying activity against methicillin-resistant *Staphylococci* but active against penicillin-insusceptible *S. pneumoniae* and, to some extent, Gram-negative bacteria). This may become critical in the near future as more new antibiotics are likely to be approved, among which solithromycin may be one of the next candidates.

## Macrolides in community-acquired bacterial pneumonia

### Spectrum of activity and resistance

Macrolide antibiotics present an attractive spectrum of activity for the treatment of CABP, covering *S. pneumoniae*, agents causing atypical pneumonia (*Chlamydomphila*, *Legionella*, and *Mycoplasma*), and *S. aureus*. They are, however, poorly active against common Gram-negative

respiratory pathogens such as *H. influenzae* or *M. catarrhalis*. Their preferential use for treatment of pneumonia caused by intracellular organisms is justified by their ability to accumulate in macrophages and other phagocytic cells [21].

On these bases, macrolides have long been considered as a suitable therapeutic option for CAPB, including in children (where fluoroquinolones are contra-indicated). Yet, at the present time, and despite the fact they still appear in many treatment guidelines (see Figure 1), the empiric use of macrolides in monotherapy for typical pneumonia is questionable because of the high resistance rates of *S. pneumoniae* reported in several countries all over the world (>80% in Asia [22], 15–40% in the USA or in most European countries [23,24], and 20% in Canada [25]). This may apply also to atypical pneumonia in regions where resistance rates of *M. pneumoniae* to macrolides have reached alarming figures (10% in the US [26] and up to 40% in Asia [27] with higher levels locally). High-level resistance to macrolides proceeds from modifications of their ribosomal target by methylation, leading to the MLS<sub>B</sub> phenotype (cross-resistance to macrolides, lincosamides, and streptogramins B). Expression of methylases can be constitutive (affecting all macrolides) or inducible (by 14- and 15-membered macrolides). Low-level resistance is mediated by active efflux and has been mainly described in *S. pneumoniae* [28]. Of note, active efflux by broad spectrum transporters of the RND superfamily (Resistance Nodulation Division) accounts for the intrinsic resistance of many enteric Gram-negative organisms to macrolides.

Other drawbacks of macrolides include the high risk of drug interactions (due to their potent inhibitory activity on cytochromes P450 activity)[29], and the occurrence of many side effects, among which corrected QT interval (QTc) prolongation (especially when combined with other at-risk drugs) [30], increase in hepatic enzymes blood levels [31], and digestive discomfort due to their agonist activity on gastric motilin receptors [32] are most noteworthy.

### Clinical efficacy

Globally speaking, clinical trials and meta-analyses do not report significant difference in outcome for patients with properly diagnosed CABP and treated by a macrolide or a  $\beta$ -lactam. These studies also show equivalence or lower efficacy of macrolides when compared to respiratory fluoroquinolones (see for review [33,34]). Nevertheless, the link with the susceptibility of the offending organism to the drug administered is rarely done. A recent retrospective study conducted in Spain on 643 patients with hospitalized CABP tried to address this question and concluded that there was no difference in outcome

whether patients were infected by a macrolide-susceptible or a macrolide-resistant *S. pneumoniae*, irrespective of the fact their treatment included or not a macrolide. Yet, only 2% of patients infected by a macrolide-resistant strain were actually treated by macrolide in monotherapy [35], severely limiting the value of the demonstration.

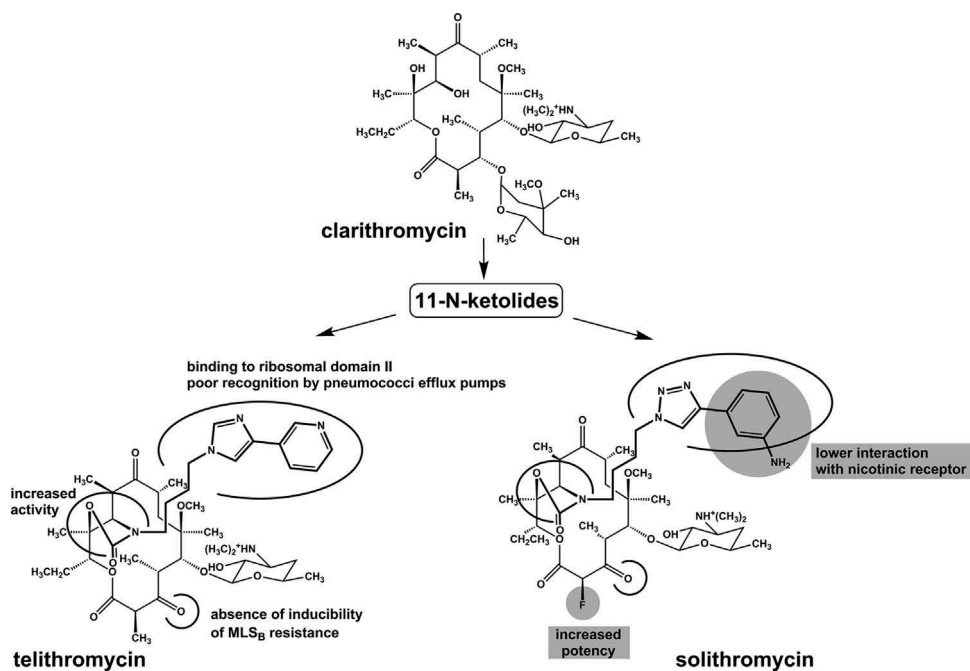
In most CABP guidelines, monotherapy by macrolides is reserved for outpatients with mild infection whereas they are usually combined to a  $\beta$ -lactam for more severe cases requiring hospitalization. In these cases, macrolides are actually used to extend the spectrum of the therapy towards intracellular pathogens (while the  $\beta$ -lactam acts as the main anti-pneumococcal agent) and, possibly also, for their immunomodulatory effects [36]. The latter have, however, been better documented in ventilator-associated, hospital-acquired pneumonia [33]. Several clinical studies concluded to the benefit of the combination of macrolides with  $\beta$ -lactams for reducing mortality or length of stay in ICU for severely ill patients (see [37] for review). Among the most recent ones, an open-label, multicenter, noninferiority, randomized trial compared  $\beta$ -lactam monotherapy to macrolide/ $\beta$ -lactam combination in 580 patients with hospitalized CABP. The authors conclude that (i) there was a nonsignificant trend to a better outcome for the combination in patients with severity index category IV, (ii) combination therapy was superior in the subgroup of patients with atypical pathogens, and (iii) noninferiority of the monotherapy was observed in other situations [38]. Another recent study

in a pediatric population showed a lower rate of therapeutic failures with combined therapy compared with  $\beta$ -lactam monotherapy in children aged of >6 years, which was ascribed to an effective coverage of intracellular pathogens [39].

## Ketolides and solithromycin

### Chemical structure and structure–activity relationship in relation with pharmacological profile

Ketolides are a subclass of the macrolide antibiotics, among which telithromycin is the only approved molecule so far. Compared to macrolides, ketolides present three specific chemical features, namely (i) a lack of the 3-O-cladinose sugar (replaced by a keto group, hence their name), (ii) a 11,12- or 6,11-cyclic moiety, and (iii) a heteroaryl-alkyl side chain attached to the macrocyclic ring through a suitable linker (see Figure 2). These modifications modify their antimicrobial properties in relation to resistance in the following way (see [40,41] for reviews). First, the removal of the cladinose largely decreases the affinity for the main binding site of macrolides but it also makes the corresponding derivatives insusceptible to the methylation of this site (responsible for a main mechanism of resistance to macrolides). In addition, the absence of cladinose makes ketolides unable to induce the



**Figure 2.** chemical structure of solithromycin, as compared to telithromycin (other ketolide already on the market) and clarithromycin. The modifications brought to ketolides as compared to macrolides are circled in black; differences between telithromycin and solithromycin are highlighted on a gray background.

expression of the corresponding ribosomal methylases (so that they are potentially active against both the constitutive and the inducible phenotypes of this resistance). Second, the additional side chain of ketolides allows them to target a second binding site at domain II of the ribosomal subunit. This restores their affinity to ribosomes, conferring them very low minimal inhibitory concentrations (MICs) towards macrolide-susceptible strains (2 binding sites) and low MICs towards macrolide-resistant strains. Lastly, because of the global change in structure, ketolides are less susceptible to efflux in *S. pneumoniae* than 14- and 15-membered macrolides. While telithromycin had thus clear advantages over macrolides in terms of activity against both susceptible and resistant strains, its clinical use was quickly limited after initial approval by observation of rare but life-threatening side effects, namely acute hepatic failure and severe liver injury, visual disturbance, transient loss of consciousness, and life-threatening respiratory failure in patients with *myasthenia gravis*, all of them being acknowledged as warnings in the official labels of this drug. The mechanism for these adverse effects is not fully established, but they may result from the blockade of nicotinic acetylcholine receptors (present at the vagus nerve terminations in liver, ciliary eye ganglion, and neuromuscular junction) by the pyridine-imidazole group carried by the side chain of telithromycin [42].

In this context, a series of ketolides were developed (see [40] for a recent review), among which solithromycin (CEM-101; Cempra Inc., Chapel Hill, NC, USA; the compound was originally synthesized as OP-1068 at Optimer Pharmaceuticals [acquired by Cubist in 2013, which itself was acquired by Merck & Co. in 2014]) has now completed two Phase III clinical trials for the treatment of community-acquired pneumonia. It is also under development for the treatment of urethritis.

Solithromycin differs from telithromycin by the addition of a fluor substituent on the macrocycle (hence the subclass of fluoroketolides), which increases its antibacterial potency by contributing to tighten drug binding to the ribosome [43] and makes the molecule more stable by preventing the enolization of its keto group. But the nature of its (amino-phenyl)triazol side chain is also critical because it confers to solithromycin a 30-fold reduced affinity for the nicotinic receptors as compared to telithromycin [42] while fully maintaining the critical ketolide antimicrobial properties (i.e. the capacity to bind to mono- or di-methylated ribosomes [43], to impair ribosomal assembly [44], and to reduce the fidelity of reading frame maintenance [45]).

### Spectrum of activity

The intrinsic activity of solithromycin against streptococci and pathogens possibly causing CABP is compared to that of telithromycin and of macrolides in Table 1. As telithromycin, solithromycin shows lower MICs than macrolides against macrolide-susceptible organisms and keeps useful activity against macrolide-resistant ones. As all macrolides, it is less active against *H. influenzae* than against other respiratory pathogens. Generally speaking, MIC<sub>50</sub> and MIC<sub>90</sub> are one dilution lower for solithromycin than for telithromycin.

### Solithromycin pharmacological profile in the context of bacterial community-acquired pneumonia

#### In vitro activity in the context of CABP

The activity of solithromycin against streptococci and CABP-relevant pathogens is summarized in Table 1 based on published studies. It is still continuously evaluated against clinical isolates, and the susceptibility data have not changed over the last years, confirming an appropriate profile for the treatment of CABP. The last survey (presented as a poster) studied a huge collection of isolates assembled in 2014 and including a large proportion of respiratory samples [51]. It shows MIC distributions similar to those previously published (summarized in Table 1), with even lower values for *S. pneumoniae*. Typical figures for MIC<sub>50/90</sub> are 0.008/0.12 mg/L against 1713 *S. pneumoniae*, 0.06/0.12 mg/L against 577 *M. catarrhalis* (all but one  $\leq 0.25$  mg/L), 1/2 mg/L against 1308 *H. influenzae* (99.2%  $\leq 4$  mg/L), and 0.06/ $>32$  mg/L against 1024 *S. aureus* (85.3%  $\leq 1$  mg/L). Likewise, in a collection of 732 clinical isolates of *S. pneumoniae* enriched in strains resistant to antibiotics currently used to treat respiratory tract infections (macrolides, fluoroquinolones, and  $\beta$ -lactams), solithromycin shows similarly low MICs (MIC<sub>50/90</sub> 0.016/0.06 mg/L), no cross-resistance with the comparators, except for telithromycin (but for which resistance rates are low [2.9%] and MICs are usually 1 log<sub>2</sub> dilution higher than those of solithromycin) [52]. Moreover, in contrast to conventional macrolides which are considered as bacteriostatic agents, solithromycin showed bactericidal activity, including against macrolide-resistant pneumococci, among which 2/3 (n = 33) have a MIC/MBC ratio  $\leq 4$ , unrelated to the serotype of the strain or to the solithromycin MIC [53]. With respect to *S. aureus*, the range of MICs as well as MIC<sub>50</sub> values are similar for both methicillin-susceptible and methicillin-resistant organisms (0.06–0.12 mg/L against MSSA and

**Table 1.** MIC distributions of solithromycin and telithromycin or macrolides against streptococci and other pathogens causing CABP.

Species	Nb isolates	Solithromycin		Telithromycin		Azithromycin		Clarithromycin		Reference
		Range	MIC <sub>50</sub> /MIC <sub>90</sub>	Range	MIC <sub>50</sub> /MIC <sub>90</sub>	Range	MIC <sub>50</sub> /MIC <sub>90</sub>	Range	MIC <sub>50</sub> /MIC <sub>90</sub>	
<i>S. pneumoniae</i>	150	≤0.008–0.5	0.15/0.25	≤0.008–1	0.03/0.5	0.03–>16	>16/>16	≤0.008–>16	>16/>16	[46]
<i>S. pneumoniae</i> macrolide-R	272	≤0.03–0.5	0.06/0.25							[47]
MLS <sub>B</sub> clindamycin-S	48	≤0.008–0.25	0.03/0.12	0.03–1	0.12/0.5					[46]
MLS <sub>B</sub> clindamycin-R	88	≤0.008–0.5	0.06/0.25	0.03–1	0.12/1					[46]
β-hemolytic <i>Streptococci</i> (telithromycin-S)	99	≤0.008–0.12	0.015/0.03	≤0.025–0.12	0.03/0.12	0.015–>16	0.12/>16	≤0.008–>16	0.03/>16	[46]
β-hemolytic <i>Streptococci</i> (telithromycin-R)	44	≤0.015–1	0.12/0.5	2–>4	4/>4					[46]
<i>S. viridans</i>	51	≤0.008–0.12	≤0.008/0.06	≤0.008–0.5	0.015/0.25	≤0.008–>16	0.12/4	≤0.008–8	0.03/2	[46]
<i>S. aureus</i> (all)	180	0.06–>16	0.06/>16	0.12–>16	0.06–>16					[48]
A.12.MSSA	75	0.06–>16	0.06/0.12	0.06–>16	0.12/0.25					[48]
A.12.HA-MRSA	75	0.12–>16	0.12/>16	0.25–>16	0.06/>16					[48]
A.12.CA-MRSA	30	0.06–0.12	0.12/0.12	0.12–0.5	0.25/0.25					[48]
<i>C. pneumoniae</i>	10	0.25–1	0.25/0.25	0.015–0.25	0.06/0.06	0.015–0.125	0.125/0.125	0.015–0.125	0.06/0.06	[49]
<i>H. influenzae</i> β-lactamase-	52	0.5–4	1/2	1–16	2/4	0.5–4	2/2	4–16	8/8	[46]
<i>H. influenzae</i> β-lactamase+	48	0.12–4	1/2	0.25–8	2/4	0.25–4	1/2	0.25–16	8/8	[46]
<i>M. catarrhalis</i>	21	≤0.008–0.5	0.12/0.12							[46]
<i>L. pneumophila</i> serogroup 1	196	≤0.015–0.0625	≤0.015/0.03			≤0.0625–2	0.125/1			[50]

MRSA), but MIC<sub>90</sub> are much lower against MSSA or community-acquired MRSA (0.06 to 0.12 mg/L) than against hospital-acquired MRSA (>16 mg/L) [48,51]. Interestingly also, solithromycin was effective against *S. pneumoniae* growing in biofilms *in vitro*, although to a lesser extent than fluoroquinolones [54], as well as against the intracellular forms of *L. pneumophila* or *S. aureus* [55].

## Pharmacology

### Pharmacokinetics

The pharmacokinetic profile of oral solithromycin has been described in healthy volunteers (Table 2) [56]. The oral bioavailability of solithromycin is approx. 67% and is similar in fasted and high-fat fed individuals [56]. As other macrolides, solithromycin displays a broad tissular distribution, related to its capacity to accumulate within eukaryotic cells [55]. More specifically in the context of

CABP, solithromycin widely distributes in alveolar macrophages (24 h-AUC: 1500 mg × h/L; ratio to serum concentration: 180) and epithelial lining fluid (ELF) (24 h-AUC: 80 mg × h/L; ratio to serum concentration: 10) [57]. Moderate accumulation occurs after 7 days of dosing, which likely reflects progressive inhibition of its own metabolism by cytochrome CYP3A4. A loading dose may allow reaching more rapidly steady-state concentrations when used by oral route [56] but is not needed upon intravenous administration [58].

Solithromycin elimination half-life (6.65 h) is slightly shorter than the terminal half-life of telithromycin (7–10 h) despite a higher degree of protein binding (85% for solithromycin vs. 70% for telithromycin [21]), but still sufficient to allow for a once-daily administration [59].

Pharmacokinetics of solithromycin by intravenous route have only been published as an abstract, which concludes that plasma concentrations reach values of ~4 µg/mL after administration of 800 mg, with global exposure 1.3–3-fold higher than that observed with equivalent oral doses [60].

Because solithromycin main elimination route is via hepatic metabolism, its pharmacokinetics were studied in patients with impaired liver function. In those showing mild or moderate impairment (Child–Pugh class A or B), total exposure to solithromycin at steady state (AUC) is similar to that observed in control subjects, but

**Table 2.** Pharmacokinetic profile of oral solithromycin in healthy volunteers [56].

Parameter	Single daily dose		Multiple dose
	400 mg (fast/fed)	800 mg	400 mg/day (day 1/day 7)
C <sub>max</sub> (mg/L)	0.61/0.63	1.32	0.58/1.09
T <sub>max</sub> (h)	3.5/3.5	3.5	3.5/4
AUC (mg × h/L)	5.47/5.08	13.67	4.84/13.27
T <sub>1/2</sub> (h)	5.37/5.02	6.65	4.82/7.47

lower in individuals with severe hepatic impairment (Child–Pugh class C) [61], possibly related to a higher body mass index in the specific group of patients investigated. No dosage reduction is proposed based on hepatic function.

### Pharmacodynamics

Ketolides are considered as AUC/MIC-dependent antibiotics (see [21] for review). A mice pneumonia model allowed to determine the values of this parameter that are predictive of efficacy. Thus, ELF/free plasma AUC<sub>0–24h</sub>/MIC ratios associated with bacteriostasis and with a 1 and 2 log<sub>10</sub> CFU reduction from baseline were 1.26/1.65, 15.1/6.31, and 59.8/12.8 h, respectively [62].

On this basis, the proposed therapeutic scheme by oral route, which consists in a loading dose of 800 mg followed by a 4-day treatment with a daily dose of 400 mg, allows to reach an AUC/MIC > 1.3 in ELF with a probability of 99.9% of covering for organisms with an MIC as high as 1 mg/L [59], with C<sub>max</sub> and AUC of approx. 1.3 mg/L and 14 mg × h/L (for a 800-mg dose) and of approx. 0.8 mg/L and 7 mg × h/L (for a 400-mg dose; Table 2). This target was also reached if administering 400 mg daily intravenously, with no need, however, for a loading dose [58].

Macrolides being frequently used for the treatment of respiratory tract infections in pediatrics, solithromycin pharmacokinetics were also evaluated in 13 adolescents with suspicion of infection and aged from 12 to 17 years [63]. They received a median dose of 800 mg (range 400–800 mg) on day 1 and of 400 mg (range 200–400 mg) on days 2–5 and showed similar exposure as adults receiving the same doses, as well as good tolerance.

### Anti-inflammatory effects

As other macrolides, solithromycin shows, in addition to its antibacterial properties, anti-inflammatory effects *in vitro* or in animals. Although more relevant of the pathophysiology of COPD, these effects have however also been claimed to participate to the favorable outcome observed with macrolides in patients suffering from CABP [36]. Thus, using cultured cells and/or peripheral blood mononuclear cells from COPD patients, solithromycin inhibits *in vitro* the production of TNF $\alpha$  and CXCL8, the activity of MMP9, and the activation of NF- $\kappa$ B by oxidative stress [64]. More specifically in the context of COPD, solithromycin can also restore better than other macrolides the sensitivity to corticosteroid treatments by stimulating histone deacetylase-2 activity via an inhibition of the phosphoinositide 3-kinase pathway [65].

### Safety profile

No specific toxicity has emerged from the analysis of the phase 2–3 trials, the most frequently reported adverse reactions being gastrointestinal disorders and hepatic enzymes elevations (see details in the next section). Moreover, a Phase 1, single center, 3-way cross-over, placebo- (intravenous 0.9% sodium chloride) and active- (moxifloxacin 400 mg orally) controlled, double-blind, randomized trial was conducted on a total of 48 subjects in order to compare the risk for QTc prolongation [66]. After administration of solithromycin 800 mg intravenously, the largest solithromycin  $\Delta\Delta$ QTcF that was observed at 4 h was of only 2.8 ms (upper bound, 90% CI, 4.9 ms), leading to the conclusion that solithromycin had no clinically meaningful effect on the key cardiac conduction parameters namely the PR and QRS intervals.

### Solithromycin in bacterial community-acquired pneumonia

Three clinical trials have been performed with solithromycin in order to evaluate its efficacy and safety for the treatment of CABP.

### Phase II trial

The first one is a randomized, double-blind, multicenter Phase II study (NCT01168713) comparing oral solithromycin (800 mg once daily on day 1 followed by 400 mg once daily on days 2–5) with oral levofloxacin (750 mg once daily on days 1–5) [67]. Patients were from 30 clinical centers (26 in the United States and 4 in Canada) and randomized to a treatment arm in a 1:1 ratio for solithromycin or levofloxacin after stratification for age and pneumonia severity index (PORT score). Inclusion criteria were male or female patients older than 18 years with a PORT risk class of II–IV (50 < PORT  $\leq$  105), capable of taking a drug orally and presenting at least 3 of the following symptoms: cough with production of purulent sputum or change in sputum characteristics consistent with a bacterial infection, dyspnea or tachypnea, chest pain due to pneumonia, fever, rales, and/or evidence of pulmonary consolidation. Acute bacterial pneumonia diagnostic was confirmed by a chest radiograph or computed thorax tomography performed within 48 h before the administration of the first dose of antibiotic. Exclusion criteria related to the patient included subjects with ventilator-associated pneumonia or any other known cause of pulmonary or bronchial obstructive disease (COPD grade IV), history of hospitalization within 90 days, or



residence in a long-term-care facility within 30 days prior to the onset of symptoms, known HIV, hepatitis B virus, or hepatitis C virus infection. Drug-related exclusion factors included any condition that could affect drug absorption, patient at risk of cardiac adverse effects (heart rate-corrected QT interval (QTc) of > 450 ms or current use of drugs known to prolong the QT interval), intolerance or hypersensitivity to fluoroquinolone or macrolide antibiotics, and history of tendonopathy with fluoroquinolone use or of *myasthenia gravis*. Moreover, patients could not have received any prior systemic antibacterial therapy for the current CABP episode, unless there was clinical evidence of treatment failure and/or isolation of a resistant pathogen while on the prior therapy. From the 132 randomized patients, 64 and 68 received solithromycin and levofloxacin, respectively, among which 55 and 58 were clinically evaluable; 16 versus 11 patients suffered from COPD.

A pathogen was isolated in only 32 patients, among whom 18 in the solithromycin group (7 *S. pneumoniae* and 2 other streptococci, 1 *S. aureus*, 3 *H. influenzae* and 1 *H. parainfluenzae*, 1 *M. catarrhalis*, 1 *C. pneumoniae*, 1 *M. pneumoniae*, and 1 *Klebsiella oxytoca*), and 14 in the levofloxacin group (3 *S. pneumoniae* and 2 other streptococci, 3 *S. aureus*, 4 *H. influenzae*, 1 *M. catarrhalis*, 1 *C. pneumoniae*, and 2 *Klebsiella pneumoniae*). All strains were susceptible to both antibiotics except the two *K. pneumoniae* strains, which were resistant to solithromycin only.

Clinical success at the test-of-cure visit (4–11 days after the last dose) were comparable in the intent-to-treat (ITT) (84.6% for solithromycin vs. 86.6% for levofloxacin) and microbiological-intent-to-treat (micro-ITT) (77.8% for solithromycin vs. 71.4% for levofloxacin) populations. Early response success rates at day 3 (improvement in at least two symptoms of pneumonia) were also comparable (72.3% for solithromycin vs. 71.6% for levofloxacin). Focusing on the microbiologically-evaluable ITT population, failure was observed in 3 patients infected by *S. pneumoniae* (among which one considered as failure only because missing the EOT visit) and 1 patient infected by *H. influenzae* and suffering from asthma in the solithromycin group. In the levofloxacin group, failure was observed in 1 patient co-infected by *S. pneumoniae* and *H. influenzae* discovered after inclusion to be HIV positive and in another patient infected by *S. pneumoniae* only. With respect to safety, treatment-emergent adverse events were more frequent in patients treated with levofloxacin (13/68; 19.1%) than with solithromycin (7/64; 10.9%) and concerned mainly mild or moderate gastrointestinal symptoms that led to treatment discontinuation in six levofloxacin-treated patients. Grade 3 elevation in

alanine aminotransferase and aspartate transaminase were observed in one to two patients in each group but were reversible after the end of the treatment. Globally, this study documented the efficacy and safety of solithromycin in CABP and supported its further evaluation in Phase III trials for this indication.

### Phase III trials

Two randomized, double-blind, multicenter Phase III trials have been recently completed. Trial NCT01756339 (SOLITAIRE-ORAL) compared solithromycin (800 mg orally on day 1 followed by 400 mg daily on days 2 through 5, followed by placebo on days 6 and 7) to moxifloxacin (400 mg orally on day 1 to 7) for efficacy and safety in the treatment of CABP. Trial NCT01968733 (SOLITAIRE-IV) compared the same drugs given by intravenous route with potential step-down to oral route.

In SOLITAIRE-ORAL, 860 patients were randomized 1:1 to solithromycin or moxifloxacin after stratification for geographic region (16 countries; number of patients: Europe: 448; Latin America: 106; North America: 204; South Africa: 102), history of asthma and/or COPD, and PORT score (II vs. III/IV; limits set at >50 and ≤105). ITT populations consisted in 424 and 432 patients treated by solithromycin and moxifloxacin, respectively. With respect to inclusion and exclusion criteria, patients had to present an acute onset or worsening of at least 3 of 4 cardinal symptoms (cough, dyspnea, chest pain, and sputum production), have fever or hypothermia, and/or physical examination findings consistent with CABP. Diagnostic had to be confirmed by chest radiograph showing lobar or patchy parenchymal pulmonary infiltrates. Pneumonia could not be hospital- or healthcare-associated and no long-acting antibiotic could have been taken by the patient during the previous 7 days. A pathogen was identified in 54% of the patients, among which the most prevalent were *S. pneumoniae* (23%), *H. influenzae* (16%), *L. pneumophila* (15%), *M. pneumoniae* (9%), *M. catarrhalis* (6%), and *S. aureus* (4%) [68,69]. Pneumococci belonged to various serotypes (38% non-vaccinal serotypes; more than 60% serotypes present in the 23-valent vaccine for European and Latin America isolates) [68]. Solithromycin was noninferior to moxifloxacin irrespective to infection severity score, patient's history of asthma or COPD, or age (78.2% vs. 77.9% success rate for solithromycin and moxifloxacin, respectively; difference + 0.29% [confidence interval (CI): -5.5, 6.1] at the early evaluation [day 4] and 84.5% versus 86.6%; difference -2.13% [CI: -7.1, 2.8] at the short follow-up visit [day 12–17]). There was a nonsignificant trend to higher success rate in

patients aged >75 years (83.9% vs. 69.8% success rate for solithromycin and moxifloxacin, respectively; difference +14.03% [CI: -2.1, 30.2] at the early evaluation [day 4]). At the short-term follow-up visit (day 12–17), solithromycin was noninferior to moxifloxacin, with numerical values higher in patients aged 65–74 years (+2.48% [CI: -8.3, 13.3]) or >75 years (+1.36% [CI: -12.8, 15.5]) as well as in patients with history of asthma or COPD (ITT population: +6.00% [CI: -6.5, 18.5]) [70,71]. A subanalysis of patients infected by *C. pneumoniae* showed very low solithromycin MIC<sub>90</sub>, (0.000032 mg/L vs. 0.125 mg/L for moxifloxacin), including for strains resistant to azithromycin, associated with a similarly high treatment success rate (89.2% vs. 90.5% for solithromycin vs. moxifloxacin) [69].

Treatment-emergent adverse effects were reported in about one third of the patients in both arms, with the most frequent being headache (4.5% vs. 2.5% of patients treated by solithromycin and moxifloxacin, respectively), diarrhea (4.2% vs. 6.5%), nausea (3.5% vs. 3.9%), emesis (2.4% vs. 2.3%), and dizziness (2.1% vs. 1.6%). Grade 3 (3–8× upper limit of normal [ULN]) and Grade 4 (>8× ULN) elevations in transaminases were noticed in 4.6% versus 2.1% and 0.7% versus 1.2% of patients treated by solithromycin and moxifloxacin, respectively [70,71]. Two cases of *Clostridium difficile* infections were recorded in the moxifloxacin arm. This study allowed to conclude that oral solithromycin given for 5 days is noninferior to oral moxifloxacin given for 7 days for the treatment of CABP, with numerically higher number of successful treatments in aged patients and in patients with specific comorbidities (asthma or COPD), who represent two populations at higher risk for CABP morbidity and mortality.

The SOLITAIRE-IV trial was completed in September 2015 but its results have not yet been released.

### Expert commentary

The impact of pneumonia on human health is high worldwide. The World Health Organization estimates that it caused more than 3 million deaths in 2012, the most fragile populations being children below 2 years of age and people living in low-income countries [72,73]. It also represented the second leading cause of disability-adjusted life years in 2010 [74]. These alarming figures emphasize the necessity of selecting and using an optimal empiric therapy as early as possible [15]. Desirable properties for a first-line empiric antibiotic comprise (a) a spectrum of activity covering the main pathogens involved in the pathology, irrespective of the expression of mechanisms of resistance; (b) an established efficacy in the target

population; (c) a demonstrated safety profile, including in fragile populations at risk for the disease (young children and elderly patients); (d) a low potential for drug interactions; and (e) an oral route of administration. Based on their spectrum of activity and favorable pharmacokinetics, ketolides may represent an appropriate choice. Nonetheless, the toxicities observed with telithromycin discredited this class of drugs [75] and led the registration authorities to revise their guidance on the way to conduct clinical trials with antibacterial agents in order to insure their efficacy, usefulness, and safety [76]. In this context, the completion of the clinical development of solithromycin for the treatment of CABP is an example of sound strategy that renewed the interest in the ketolide class [77]. The impressive intrinsic activity of this molecule on pneumococci and agents causing atypical pneumonia, including strains resistant to macrolides and other antibiotic classes, its efficacy comparable to that of respiratory fluoroquinolones in Phase II/III trials together with its convenient scheme of administration and remarkable pulmonary disposition concur to convincingly support the potential of this molecule as a monotherapy for the empirical treatment of CABP [78]. Additional data are required, however, to document its efficacy in severe cases and/or for inpatients. We also need to balance the benefits outlined so far against the known drawbacks of macrolides/ketolides, especially when considering what has been observed in postapproval studies for telithromycin. At this stage, no specific sign indicative of possible development of severe toxicities has been noticed in patients treated by solithromycin. Moreover, *in vitro* studies tend to suggest that the rare but severe adverse effects observed with telithromycin are less likely to occur with solithromycin. The label of telithromycin reports an incidence of 7 cases of telithromycin-induced hepatitis per 10,000 patients treated, that is, a number of patients needed to treat of 1429 for one occurrence. This figure roughly corresponds to the number of patients that has been exposed to solithromycin during Phase I–III trials. Although no sign of major liver dysfunction has been evidenced so far, it is obvious that careful surveillance should be maintained and be part of registration package if the drug is approved for clinical use in order to promptly detect similarly rare but severe adverse events, should they occur with solithromycin.

### Five-year view

Industry investment in pneumonia research has been relatively low at the end of the twentieth century in

spite of its continuous burden for public health [79]. Yet, a few molecules in Phase II/III in the class of ketolides as well as of quinolones bear witness to a regain of interest in this field [40]. Ketolide development was, however, considered as a high-risk venture because of story of telithromycin (severe indications restrictions after original approval because of risk of hepatotoxicity). In this context, solithromycin's overall profile looks particularly promising and valuable [78], opening new perspectives for the future of this class of antibiotics. Further attesting the clinical interest for this drug, the US FDA granted a 'Qualified Infectious Disease Product' (QIDP) status and a 'Fast Track Designation' path to Cempra for solithromycin in the treatment of CAPB in August 2015. This status facilitates the development and expedites the review of new drugs that are intended to treat serious or life-threatening conditions and that demonstrate the potential to address unmet medical needs. It also gives a 5 years extension of commercial exclusivity in the US (GAIN act) over what is the case under the provisions of the Hatch-Waxman Act (possibility for FDA to approve generics upon patent expiration of the original molecule based on Abbreviated New Drug Application [i.e. without clinical assessment]). Should solithromycin come on the market in a near future, this would be an additional, forceful argument for stimulating competent instances to revise guidelines, especially in countries that still consider macrolides as first-line therapy in spite of evidence of local large resistance rates. Yet, we have to keep in mind that reserving new antibiotics for patients who really need them is the best way to insure them a long life by minimizing the risk of emergence of resistance and unnecessarily exposing patients to adverse effects. With respect to the first issue, a still missing critical piece of information is the susceptibility

breakpoints for solithromycin that will be established by the FDA upon approval in the USA and by the European Committee on Antimicrobial Susceptibility Testing for approval by the European Medicines Agency. With respect to toxicity issues, careful pharmacovigilance follow-up will be critical in order to confirm the so-far clear safer profile of the drug compared to telithromycin when used on a larger scale than what is feasible during the registration studies.

The fluoroquinolone nemonoxacin was also granted QIDP and fast-track designations for CABP by the FDA in December 2013 [40]. Fluoroquinolones share with ketolides excellent biodistribution, activity on both pneumococci and intracellular bacteria and, for new generation molecules, activity on strains resistant to older ones. They differ, however, in their safety profile, putting possibly patients at higher risk of cardiac arrhythmias, tendinopathies, dizziness, or *C. difficile* colitis [80]. Thus, balancing efficacy and safety will probably be a key determinant in the positioning of these new drugs in our future therapeutic arsenal for the treatment of CAPB.

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#### Key issues

- Solithromycin is the first fluoroketolide with extensive preclinical and almost complete clinical development. As other ketolides, it binds to domains II and V of 50S ribosomal subunit; its fluor substituent further increases its affinity for its target and stabilizes the molecule.
- Solithromycin shows low MICs against pneumococci (including macrolide-resistant strains), intracellular pathogens causing atypical pneumonia (*C. pneumoniae*, *M. pneumoniae*, *L. pneumophila*), and *S. aureus*, but, as other macrolides, it is poorly active against *H. influenzae* and *M. catharralis*.
- As for other ketolides, solithromycin efficacy is best predicted by free AUC/MIC ratio in serum, a value of 1.6 for this ratio allowing to reach a bacteriostatic effect in a murine model of pneumonia.
- *In vitro* data show that solithromycin has a 30-fold lower affinity for nicotinic receptors than telithromycin. This interaction is thought to be critical for telithromycin toxicity (acute hepatic failure and severe liver injury, visual disturbance, transient loss of consciousness, and life-threatening respiratory failure in patients with *myasthenia gravis*).
- In clinical trials, solithromycin has been successfully used by both oral and intravenous routes, at a daily dose of 400 mg (with a 800 mg loading dose at day one when used orally) for a treatment duration of 5 days, with no need for dose adjustment in case of hepatic insufficiency.
- Solithromycin has completed one Phase II and two (SOLITAIRE-ORAL and SOLITAIRE-IV) Phase III clinical trials for the treatment of community-acquired bacterial pneumonia with levofloxacin (Phase II) or moxifloxacin (Phase III) as comparators.
- In these trials, solithromycin was noninferior to the comparator and safe, with a nonsignificant trend to higher success in elderly patients or patients suffering from COPD or asthma in the oral Phase III trial. Results from the intravenous Phase III trial have not yet been released.
- FDA granted Qualified Infectious Disease Product and Fast Track Designations to Cempra for solithromycin in the treatment of CAPB in August 2015.

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