Letter to the Editor

Solithromycin commentary

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Provenance: This is an invited Letter to the Editor commissioned by Editor-in-Chief Xi-Hua Liu, MD (Chinese Research Hospital Association, Beijing, China).

Response to: José RJ. Next generation macrolides for community-acquired pneumonia: will solithromycin rise to the occasion? Ann Res Hosp 2017;1:11.

Mandal A, Sahi PK. Solithromycin for community acquired pneumonia in adults. Ann Res Hosp 2017;1:14.

Metersky ML, Huang Y. Ketolide antibiotics: will they ever be used for community-acquired pneumonia? Ann Res Hosp 2017;1:16.

Menéndez R, Méndez R. Solithromycin: the future of macrolide is now. Ann Res Hosp 2017;1:22.

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The collective commentaries by José, Meterskey and Huang, Mandal and Sahi, and Menéndez and Méndez (1-4) emphasize the significant disease burden of community-acquired pneumonia (CAP) and the unmet need for alternative antimicrobials for the management of this potentially life-threatening infection. Present guideline recommendations list two options of antimicrobial therapy for serious infections: monotherapy with a fluoroquinolone and combination therapy with a beta-lactam and a macrolide (5). There are disadvantages to both of these treatment regimens. With fluoroquinolones, there are concerns for collateral damage in the form of several adverse effects, including an adverse effect on the gastrointestinal microbiome. For combination therapy, there is the inconvenience of two drugs and the dilemma of de-escalation from IV to oral therapy (i.e., does the patient need to step down to two oral agents). Thus, a monotherapy agent which has efficacy against the likely pathogens of CAP and is available as once-daily dosing in both IV and oral formulations would be a welcome addition to our antimicrobial armamentarium.

The need for an effective alternative to available macrolides is emphasized by the increasing resistance of *Streptococcus pneumoniae*, the most common bacterial cause of CAP. Recent surveillance studies put resistance rates to available macrolides at >40% in the United States (6). Solithromycin is active against macrolide-resistant *S. pneumoniae* and macrolide-resistant *Mycoplasma pneumoniae*, so provides activity for the most common CAP pathogens for which there is concern for resistance (7,8). In addition, solithromycin has little activity against enteric bacilli and, therefore, should have less harmful effects on normal gut flora than fluoroquinolones (9). A negative thorough-QT study, showing that solithromycin has no intrinsic propensity to prolong the QT interval, also differentiates it from other macrolides and fluoroquinolones (10).

The commentary by José expresses concern that "the widespread use of new macrolides, which will likely lead to the development of solithromycin-resistant bacterial isolates." (1). While we certainly acknowledge that use may lead to resistance, there is evidence that resistance is less likely to occur with solithromycin due to several factors: (I) a mechanism of action involving three sites on the bacterial ribosome and, therefore, requiring multiple mutations to develop resistance (11); (II) *in vitro* passaging studies indicating that resistance in *S. pneumoniae* is difficult to develop after repeated exposures (unpublished data); (III) with a planned indication for CAP and not for less severe respiratory tract infections (e.g., chronic bronchitis, sinusitis), the overall amount of use will be limited compared to agents which also may be used for these infections.

As reviewed by the commentaries, solithromycin has been shown to be non-inferior to moxifloxacin and has had a safety profile which was found to be acceptable in phase 3 clinical trials. Although there was an observed increase

in liver enzymes, these increases were asymptomatic and transient, with no evidence of significant drug-induced liver injury in CAP patients. However, the past association of liver toxicity of a prior ketolide, telithromycin, no doubt had an influence on the FDA decision to request additional liver safety data prior to approval. A phase 3 CAP study utilizing a 7-day oral dosing regimen of solithromycin is currently enrolling in Japan (conducted by Toyama Chemical Co., Ltd., Tokyo) and will provide additional safety and efficacy data in adults with CAP. Solithromycin is also currently being evaluated in pediatric patients with CAP, aged 2 months to 17 years (NCT02605122). We believe the potential for both IV and oral formulations and a targeted spectrum of activity against common respiratory pathogens suggests that solithromycin will be a useful monotherapy for patients with CAP.

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None.

Footnote

Conflicts of Interest: TM File Jr was an investigator in the Solitaire-IV trial and has served as a consultant for Cempra, Inc. BD Jamieson is an employee of Cempra, Inc.

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