

## Solithromycin as A Potential Novel Antibiotic Against *Neisseria Gonorrhoeae* Resistance

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### ABSTRACT

Gonorrhea is one of the most often sexually transmitted infection in the world. In 2016, WHO stated the Southeast Asia region as the fourth-highest incidence rate and prevalence of gonorrhea. One of the current problems with gonorrhea is related to its emerging resistance to first-line drugs such as cephalosporins, macrolides, and fluoroquinolones. This resistance has an impact on the difficulty of finding effective antibiotics to eradicate the infection, thus risking financial loss and infertility in sexually active age patients. This literature review will discuss solithromycin, the first fluoroketolide in phase III clinical trial, and show its potential as a new antibiotic against infection with resistant *Neisseria gonorrhoeae*. Literatures are searched using Pubmed and Google Scholar search engines with keywords: antibiotics, CEM-101, clinical trial, *Neisseria gonorrhoeae*, new treatment, pharmacology, pharmacokinetics, resistance, safety, and solithromycin. This semisynthetic antibiotic is supported by a different chemical structure from previous macrolides; improving solithromycin becomes more stable and able to bind easier with bacterial ribosomes. Pharmacologically, solithromycin provides an advantage in its high bioavailability, easy oral administration route, wide distribution, metabolism mainly in the liver, but not required dosage adjustments due to hepatic impairment, and a single dosage preparation that can increase patient compliance in healing gonorrhea infections. Also, its lower MIC50 than previous antibiotics makes it well-tolerated, therefore making this antibiotic as a potential recommendation for the management of multi-drug resistant gonorrhea in the future. Solithromycin is not inferior to the standard therapy (ceftriaxone and azithromycin), with 80% vs. 84% gonorrhea eradication rates. Per the anatomic site, the eradication rate is 92% in genital, 94% in the pharynx, and 83% in the rectum. However, special attention needs to be paid to the side effects of the gastrointestinal tract of solithromycin, as observed in phase III clinical trials at a dose of 1000 mg in the form of diarrhea (24%) and nausea (21%).

**Keywords:** antibiotic, CEM-101, gonorrhea, solithromycin, resistance

### INTRODUCTION

Sexually transmitted infections (STIs) are a global problem with a high prevalence in developing countries. Gonorrhea (GO) is one of the most commonly reported STIs caused by *Neisseria gonorrhoeae* infection. The incidence rate of new GO infections or diagnoses in 2016 is 20 per 1,000 in women and 26 per 1,000 in men resulting in 86.9 million new cases worldwide (Rowley *et al.*, 2019). The highest incidence occurred in Africa, America,

and the Western Pacific Region, South-East Asia in the fourth place, and the lowest in Europe (Kirkcaldy *et al.*, 2019; Rowley *et al.*, 2019). In 2016, the Southeast Asia region prevalence estimates of GO was 0.7% (95% CI: 0.4–1.2%) from globally 0.9% (95% CI: 0.7–1.1%) in women, and 0.6% (95% CI: 0.3–1.1%) from globally 0.7% (95% CI: 0.5–1.1%) in men. Of the world's 30.6 million reported cases, Southeast Asia is ranked the third-highest number of GO prevalence (Rowley *et al.*, 2019).

General manifestations of GO in men is acute urethritis and in women is cervicitis that occur symptomatically or asymptotically (Marrazzo & Apicella, 2017). In addition, the site of *N. gonorrhoeae* infection is also found in the pharynx, rectum, eyes, skin, joints, and internal organs (Ndowa & Lusti-Narasimhan, 2012). The problem of GO is not only limited to various clinical symptoms or frightening complications, but also the increasing number of GO resistance (Rowley *et al.*, 2019). Drug-resistant *N. gonorrhoeae* becomes the top five urgent antibiotic-resistant threats to public health (CDC, 2019). In 1937 this bacterium began to be resistant to sulfonamides and now also occurs against penicillin, tetracycline, macrolides, and fluoroquinolone (CDC, 2012). Based on antibiotic resistance reports from 2009–2014, World Health Organization (WHO) found GO resistance to ciprofloxacin in 97% of countries and azithromycin in 81% of countries. Currently, there is also resistance to a single broad-spectrum cephalosporin antibiotic namely oral cefixime and ceftriaxone injection in 60% countries (WHO, 2017). In the Asia-Pacific region and Europe, GO infection is observed to require multiple increases in minimum inhibitory concentration (MIC) to stop infection (Chisholm *et al.*, 2010; Cole *et al.*, 2011; WHO, 2014). Recent reports from Japan regarding GO resistant to ceftriaxone have become an important alarm as a challenge in the future (Unemo *et al.*, 2012). The effects of antimicrobial resistance will harm individuals of sexually active age because of the reproductive morbidity, including pelvic inflammatory disease, infertility, and neonatal blindness in infants of infected pregnant women. Moreover, infection of *N. gonorrhoeae* can facilitate the transmission of HIV (Ndowa & Lusti-Narasimhan, 2012). Financially, high costs health services and expensive antibiotic regimens to treat GO resistant will increase patient burdens.

Current treatment options (oral cefixime, kanamycin injection, ceftriaxone injection, or ceftriaxone injection plus oral azithromycin) are also limited due to its high cost when applied to resource-poor countries with high infection loads (CDC, 2012; Ndowa & Lusti-Narasimhan, 2012; WHO, 2017; Workowski & Bolan, 2015). Alternative treatments have been offered such as spectinomycin is hard to produce and synthesize (Lahra, 2011). On the other hand, gentamicin, a “reused” drug, has been used in Indonesia and Malawi, and there have been no reports of resistance (CDC, 2006; Kamanga *et al.*, 2010).

However, clinical data supporting the application of gentamicin to fight GO resistance is still lacking, so it cannot be made a global recommendation (Brown *et al.*, 2010).

In overcoming several problems related to the limitations of therapy and increasing GO resistance, it is necessary to develop new antibiotics that are effective, safe, and affordable. Solithromycin (CEM-101) has recently become the first fluoroketolide to enter clinical development (Chen *et al.*, 2019; Hook *et al.*, 2015). This antimicrobial has shown more spectrum and potential advantages over old macrolides against many gram-negative and positive bacteria, including *N. gonorrhoeae* (Riedel *et al.*, 2015). Through this review, a comprehensive study about solithromycin in the context of GO will be reviewed based on current development research to estimate its potency in eradicating GO infection, even combating GO resistant strain.

## MATERIAL AND METHODS

This article was made by searching various English references with the level of evidence confidence of I-IV in the last ten years regarding the development of the latest drug for GO to answer the challenges of increasing resistance. Keywords used in the PubMed and Google Scholar search engines are antibiotics, *Neisseria gonorrhoea*, new treatment, and resistance by excluding the words Sexual Transmitted Disease (STD) to prevent the large literature of other sexually transmitted infections that appear in search results. The results obtained were five original (experimental) article type journals and two randomized control trials (RCTs) explaining the potential of solithromycin as a new fluoroketolide capable of overcoming GO infection. Furthermore, further searches are done regarding the use of solithromycin using additional keywords CEM-101, clinical phase trial 1,2,3, pharmacology, pharmacokinetics, safety, and solithromycin with similar inclusion criteria as the first search. Supporting literature is also searched manually with a variety of relevant keywords and by utilizing bibliography of journals previously obtained without limiting publication years. Then the collection of articles is synthesized into a comprehensive literature review.

## RESULTS AND DISCUSSION

### The Gonorrhoea Mechanism of Antibiotics Resistance

Exposure of *N. gonorrhoeae* to various antimicrobials can cause the selection of resistant

strains. Penicillin resistance in *N. gonorrhoeae* is mediated by plasmid and chromosomally by a mutation in *penA*, *ponA*, *mtrR*, *porB*, and *pilQ* genes resulted in treatment failures. The major penicillin-binding proteins (PBPs) of *N. gonorrhoeae*, PBP1 (*ponA*) and PBP2 (*penA*), catalyze peptide cross-linkages between peptidoglycan adjacent glycan strands and are the targets of penicillin action. Point mutations in PBP2 lower its acylation rate by penicillin G, resulting in reduced susceptibility to penicillin. Other PBP2 mutations, including *penA* mutations (insertion of aspartate residues at position 345); *penA* 'mosaic' alleles; and mutations in the protein carboxyl-terminal region. Also, a single nucleotide polymorphisms (SNP) in *ponA* results in the decreased acylation of PBP1 and confers high-level penicillin resistance.<sup>5</sup> Penicillin resistance is also induced by a single nucleotide deletion in the promoter region of *mtrR*, which encodes a repressor protein (MtrR), thereby resulting in overexpression of the Mtr-CDE efflux pump (Unemo & Shafer, 2014). Also, SNPs of *porB* in the outer membrane porin PorB (by amino acid substitutions at Gly-120 and Ala-121) results in a decreased influx of  $\beta$ -lactams tetracyclines into the periplasm and an increased Minimum Inhibitory Concentrations (MICs). Other mechanisms are by a *pilQ2* missense mutation (E666K) changes *pilQ* multimerization, destabilizing pore formation around the pilus of *N. gonorrhoeae*, and blocking the diffusion into the periplasm (Ropp *et al.*, 2002). Moreover Penicillinase-Producing *N. gonorrhoeae* (PPNG) isolates carry a family of related penicillinase-producing plasmids that originated in *Haemophilus parainfluenzae*, which produce a TEM-1  $\beta$ -lactamase encoded by the transposon *Tn2*. Some of them also carry a  $\beta$ -lactamase variant with an SNPs of TEM-1 at position 135 which may act as a precursor to producing an enzyme capable of hydrolyzing extended-spectrum cephalosporins (ESCs) (Unemo & Shafer, 2014). Further, ESCs, as a current treatment recommendation, are now reduced their susceptibility. Cefixime resistance is primarily caused by mosaic allele *penA* with amino changes in PBP2 (mosaic PBP2 pattern X), with only small contributions by *mtrR* and *porB*. Whereas ceftriaxone resistance is nearly equally dependent on these three genes (Ito *et al.*, 2005; Unemo & Shafer, 2014).

Penicillin and tetracycline shared common genetic mechanisms of resistance. Plasmid-mediated resistance to tetracycline is caused by the

acquisition of a *tetM*-containing plasmid, which arose by inserting a streptococcal TetM sequence into the endogenous gonococcal conjugative plasmid. The TetM protein will bind to the 30S ribosomal subunit, thereby blocking tetracycline from binding to its target (Unemo & Shafer, 2014). Other mechanisms are mutations in *mtrR* as well as by the substitution of charged amino acids at positions G120 and A121 in PorB, and mutations of 30S ribosomal protein S10 (*rpsJ*), involved in the binding of tRNA to ribosomes, modulates the affinity of tetracycline for its rRNA binding site. Meanwhile, resistance to macrolides can arise by SNPs in 23S rRNA – the binding site of macrolides, the methylation of 23S rRNA by rRNA methylases (encoded by *ermB*, *ermC*, and *ermF*) which may block the binding of macrolides to the ribosome, a *mef*- encoded efflux pump which can export macrolides out of the bacterial cell, *mtrR* mutations that enhanced antibiotic pump efflux, and the overexpression of the MacAB efflux pump to decreased macrolides susceptibility (Unemo & Shafer, 2014).

Mutations in 16S rRNA (*spc* gene) and the 30S ribosomal protein S5 (RPS5), which become the binding site of spectinomycin to inhibits translocation, may cause resistance (Galimand *et al.*, 2000; Unemo *et al.*, 2013). Besides, fluoroquinolone resistance in *N. gonorrhoeae* is caused by point mutations arising in specific DNA gyrase (*gyrA* position S91 and D95) and topoisomerase IV (*parC* positions S88 and E91), which become quinolone target to block DNA replication (Unemo & Nicholas, 2012; Unemo & Shafer, 2014). Next, resistance to sulfonamides also common due to chromosomal mutations in *folP* lowering the affinity of enzyme dihydropteroate synthase (DHPS) for sulfonamides. Furthermore, overproduce p-aminobenzoic acid (PABA) by Gonococci cause overwhelming the inhibitory effect of sulfonamides. These antibiotics can not compete with PABA for the DHPS, so tetrahydrofolate formation, which is needed for bacterial DNA synthesis, continues and even increases (Unemo & Shafer, 2014). Finally, an ineffective antibiotic group for GO is aminoglycosides because of its high resistance levels in a single mutational step, low activity, and high potential toxicity (Dillon *et al.*, 2016; Lewis, 2010). A summary of the mechanisms of *N. gonorrhoeae* is comprehensively (Figure 1).

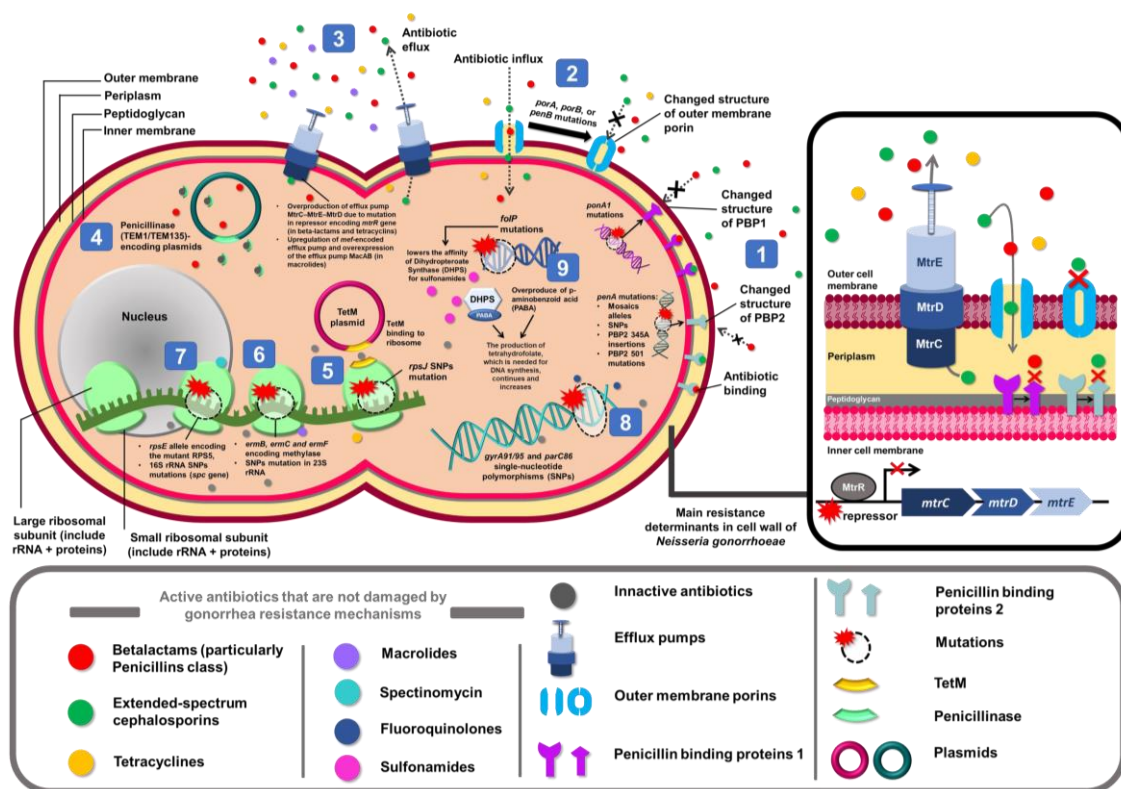


Figure 1. Resistance mechanisms of various antibiotics combating *N. gonorrhoeae* isolates. (1) Penicillin-binding proteins (PBP) mutations in beta-lactams and cephalosporins resistance; (2) Genes mutations encoding porin in beta-lactams, cephalosporins, and tetracyclines resistance; (3) Overexpression of MtrCDE pumps increase antimicrobials' efflux (beta-lactams, cephalosporins, and tetracyclines) due to repressor gene mutation, alongside upregulation of *mef*- and *macAB*-encoded efflux pumps increase macrolides efflux; (4) Hydrolyzation of the  $\beta$ -lactam ring by plasmid-encoded penicillinase in beta-lactams; (5) A single nucleotide polymorphisms (SNP) mutation in the 30S ribosomal protein (*rpsJ*) and plasmid-encoded TetM protein lower tetracyclin affinity to a ribosome; (6) 23S rRNA SNPs mutation and methylation by rRNA methylases (encoded by *erm*) block macrolides binding to the ribosome; (7) A SNP mutation in 16S rRNA and *rpsE* encoding 30S ribosomal protein S5 mutant (RPS5) inhibit spectinomycin binding to the ribosome; (8) A SNP in DNA gyrase and topoisomerase reduces binding of fluoroquinolones to these enzymes for DNA synthesis blocking; (9) DHPS-encoding *folP* mutations and overproduction of PABA impairing sulfonamides effectivity and increases production of tetrahydrofolate. (Images modified by the author) (Dillon *et al.*, 2016; Galimand *et al.*, 2000; Ito *et al.*, 2005; Lewis, 2010; Quillin & Seifert, 2018; Ropp *et al.*, 2002; Unemo *et al.*, 2013; Unemo & Shafer, 2014).

### Factors Leading to Gonorrhea Resistance

The UK Health Protection Agency shows significant differences between homosexual men, heterosexual men, and women, which reported that there was a decrease in the sensitivity of antibiotic treatment by 26%, 5%, and 1%, respectively (Ison *et al.*, 2011). Also, oral sex, especially in the context of sex work can contribute to resistance especially in the more asymptomatic pharyngeal area (Wong *et al.*, 2002). A phenomenon occurs where the antibiotic effect is less than optimal because the

infection in the pharyngeal area has already mixed with commensal bacteria that are already resistant to various antibiotics and this will result in the transfer of resistant genes to wild-type gonorrhea bacteria. Thus, people infected with pharyngeal GO can transmit resistant strains to others during oral sex (Furuya *et al.*, 2007; Saika *et al.*, 2001).

Gonorrhea resistance is common in areas where the health sector prescribes uncontrolled antibiotic use as in the case of sulfonamide antibiotic resistance (Ndowa & Lusti-Narasimhan,

2012). Also, sex workers in Asia usually consume oral quinolones as prophylaxis and this can be a contributor to antimicrobial resistance. Previous history of STI can also be a contributor to GO resistance (Cole *et al.*, 2014).

### New Therapeutic Options: Solithromycin

The ketolides are a third-generation macrolide subclass developed to fight pathogenic bacteria that are already resistant to other macrolide-class antibiotics. In ketolides, cladinose sugars present in other subclass of macrolides such as azithromycin are replaced by a ketolide ring which can bind more strongly to ribosomes and increase drug efficacy. The first drug of this subclass is telithromycin, but it has a variety of serious side effects such as visual disturbances and liver toxicity, so a new safer antibiotic is needed (Llano-Sotelo *et al.*, 2010). Solithromycin (CEM-101) is a fourth-generation macrolide from the fluoro-ketolide group that was developed to replace telithromycin. The structure of solithromycin is similar to telithromycin (Figure 2B), except in the alkyl-aryl or aromatic side chains and the presence of fluorine replacing hydrogen atoms which bind to the C-2 lactone ring. Also, unlike telithromycin, solithromycin does not have a pyridine structure. These chemical structure changes cause the solithromycin to work better and are more stable than other macrolide classes (Llano-Sotelo *et al.*, 2010).

The new ketolide was expected to overcome macrolide resistance by being able to bind strongly to domain V and weakly to domain II of 23S rRNA (Donald *et al.*, 2017). The three essential chemical structures of solithromycin include: (1) ketone (lack of cladinose group) positioned in C3 which is resistant to inducible macrolide–lincosamide–streptogramin B (MLS<sub>B</sub>)-mediated modifications and prevent methylations of the 23S rRNA domain V binding site by removing steric hindrance (similar to telithromycin), (2) aromatic/alkyl-aryl/aminophenyl side chain in C11 and C12 which provided hydrogen bond acceptor at the 23S rRNA domain II binding site (identical to telithromycin), and (3) The 2-fluorine in the C-2 lactone ring which has an interaction with the third binding site of 23S rRNA to enhance activity against telithromycin-resistant strains and also prevent C3 ketone enolization previously observed with telithromycin and other ketolides (Donald *et al.*, 2017; Fernandes *et al.*, 2016).

One mechanism of resistance to MLS<sub>B</sub> antibiotics is methylated by rRNA methylase which

encoded by the *erm* gene, known as inducible MLS<sub>B</sub> (iMLS<sub>B</sub>). Besides iMLS<sub>B</sub>, there is constitutive MLS<sub>B</sub> (cMLS<sub>B</sub>) where rRNA methylase is always produced (Donald *et al.*, 2017). The methylation triggers the chemical composition of the drug and reduces the affinity of the drug in the ribosome (Llano-Sotelo *et al.*, 2010). Solithromycin shows better activity against bacterial strains with the *erm* gene because it does not trigger iMLS<sub>B</sub>-mediated rRNA methylation, can against cMLS<sub>B</sub> through the third binding site, and C3 ketone group, and can attach to the ribosome stronger than the previous macrolides (Donald *et al.*, 2017; Llano-Sotelo *et al.*, 2010).

### Mechanism of Action of Solithromycin

A ribosome is separated into two general subunits, large (50S) and small (30S). These subunits are further split into their constituent proteins and RNAs. The 30S subunit contains 21 different proteins (S1 to S21) and a 16S RNA molecule. The 50S subunit contains 34 different proteins (L1 to L34) and two RNA molecules, a 23S and a 5S species. The three RNAs present—5S, 16S, and 23S—are critical for ribosomal function and structure, and are formed by cleavage of primary 30S transcripts and further processing (Berg *et al.*, 2002). Six domains (I–VI) are recognized in the 23S rRNA structure (Sergeeva *et al.*, 2014). The 50S RNA proteins L4 and L22 usually bind to the domain I of 23S rRNA, but mutations in these proteins may cause macrolide resistance by causing a change in the conformation of domains II, III, and V, disrupting the action of the macrolides for domain V of 23S rRNA (Ng *et al.*, 2002). Studies from Lai-King Ng *et al.*, confirmed that mutations in the *rmlA* gene within the peptidyltransferase loop of domain V of the 23S rRNA caused resistance to macrolides in *N. gonorrhoeae* (Ng *et al.*, 2002).

Solithromycin has a high affinity at its binding site of the large bacterial subunit ribosome which is composed of rRNA residues. This first interaction can inhibit protein synthesis by blocking the exit pathway of polypeptides through the exit tunnel (Llano-Sotelo *et al.*, 2010; Mallegol *et al.*, 2013). Important interactions between solithromycin and binding sites of rRNA residues are evident through biochemical examination and X-ray crystallography. Second interactions between the alkyl-aryl arm in solithromycin with base pairs and hydrogen bonding at the aminophenyl end with domain II rRNA 23S cause strong drug binding to the ribosome.

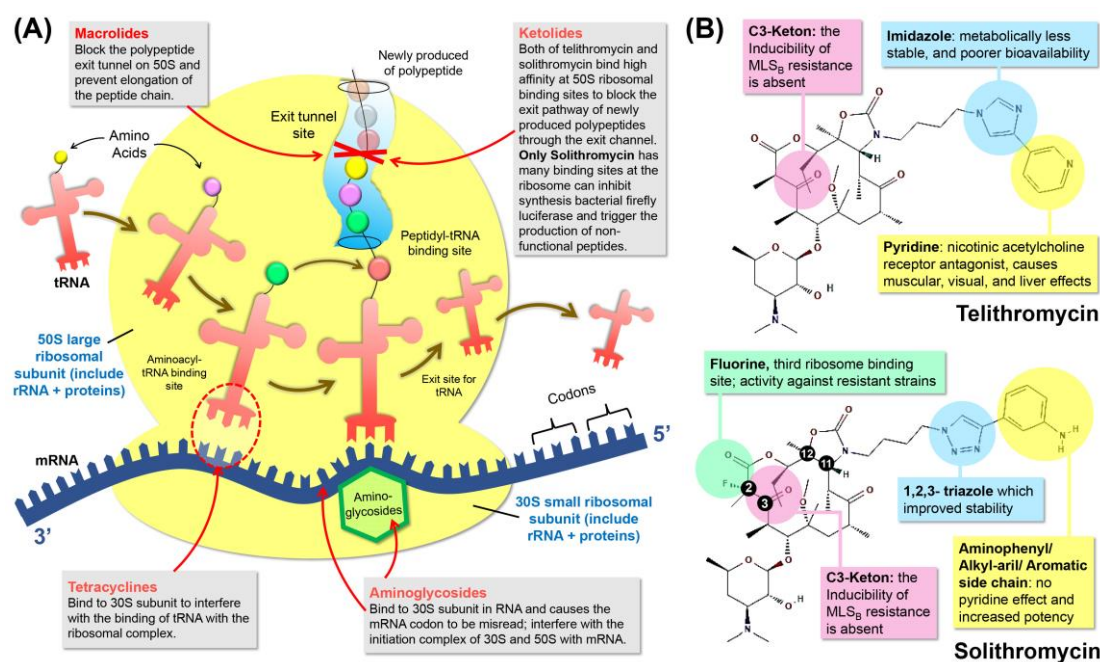


Figure 2. A Summary of the mechanism of action of several antigonococcal and differences in chemical structures between telithromycin and solithromycin (ketolides class). (A) Mechanism of action of ketolides, macrolides, tetracyclines, and aminoglycosides in eradicating GO by inhibiting protein synthesis. (B) Significant chemical structure differences between telithromycin and solithromycin which might combat resistance mechanism of GO (Images modified by the author). (Berg *et al.*, 2002; Carlson-banning & Zechiedrich, 2013; Clarkson, 2018; Donald *et al.*, 2017; Fernandes *et al.*, 2016; Ian & Marilyn, 2001; Lohsen & Stephens, 2019; NCBI, 2020a, 2020b; Ng *et al.*, 2002; Sergeeva *et al.*, 2014; Serio *et al.*, 2017; Tenson *et al.*, 2003).

Also, solithromycin binding at many bacterial ribosomal sites can prevent antimicrobial resistance (Llano-Sotelo *et al.*, 2010). Solithromycin shows a high level of selectivity in inhibiting and interfering with bacterial protein synthesis Solithromycin can inhibit the synthesis of bacterial firefly luciferase (Lux) but does not show an effect on luciferase synthesis in the eukaryotic cell translational system to a certain concentration (Llano-Sotelo *et al.*, 2010). Solithromycin can disrupt the cellular synthesis and trigger production of non-functional peptides. These mechanisms cause solithromycin to be bactericidal unlike most other macrolide-grade antibiotics (Jamieson *et al.*, 2015). A mechanism action and critical structure of ketolides (telithromycin and solithromycin) (Figure 2A).

### Development of Solithromycin Research In Vitro Research

The research study was conducted to determine the characteristics of solithromycin against several bacteria including *N. gonorrhoeae* in

2010. The study used 34 strains of *N. gonorrhoeae* with 47.1% strains resistant to penicillin, 32.4% strains resistant to tetracycline, and 14.7% resistant against ciprofloxacin. Then the bacteria were tested using solithromycin, ceftriaxone, and azithromycin. The results showed MIC<sub>90</sub> of solithromycin was 0.12 µg/mL with the ability to inhibit gonorrhea bacteria was the same as ceftriaxone but four times more potent compared to azithromycin. Also, all GO strains in this study were able to be inhibited by solithromycin to levels ≤0.25 µg/mL (Putnam *et al.*, 2011).<sup>40</sup> Other studies used 196 gonorrhea bacterial strains, showing the results of MIC of solithromycin ranged from 0.015–0.8 µg/mL, while MIC of azithromycin ranged between ≤0.031 and ≥2.048 µg/mL (Mallegol *et al.*, 2013).

Subsequent in vitro research was carried out by Golparian *et al.*, 2012 to determine the activity of solithromycin against 246 strains of *N. gonorrhoeae* including 10 strains that are highly resistant to various antibiotics recommended for GO, namely cephalosporins. The study produced

MIC<sub>50</sub>, MIC<sub>90</sub>, and MIC ranges of solithromycin are 0.125 µg/mL, 0.25 µg/mL, and 0.001–32 µg/mL, respectively, while for ketolides and other macrolides the value is higher, namely for MIC<sub>50</sub>, MIC<sub>90</sub>, and the MIC range of each value using telithromycin are 0.25 µg/mL, 1 µg/mL, and 0,001–>256 µg/mL; azithromycin each values 0.5 µg/mL, 8 µg/mL, and 0.001–>256 µg/mL; while erythromycin each values >2 µg/mL, >2 µg/mL, and 0,001–>2 µg/mL. When compared with the cephalosporin drugs, the results are slightly better. Ceftriaxone has the MIC<sub>50</sub>, MIC<sub>90</sub>, and MIC ranges of 0.016 µg/mL, 0.125 µg/mL, and <0.002–4 µg/mL; whereas for Cefixime the values are 0.032 µg/mL, 0.25 µg/mL, and <0.016–8 µg/mL, respectively (Golparian *et al.*, 2012).

The proportions of MIC levels >0.5 µg/mL in this study were 11% (n= 27), 37.8% (n= 93), and 94.3% (n= 232) respectively for telithromycin, azithromycin, and erythromycin. All isolates that are resistant to cefixime (6.5%), ceftriaxone (1.2%), ampicillin (24.4%), gentamicin, and spectinomycin (2%) are still sensitive to solithromycin. Meanwhile at 0.8% ciprofloxacin-resistant isolates and 1.2% tetracycline-resistant isolates showed MIC values of solithromycin >0.5 µg/mL, which is only 2.4% (n= 6) of all bacterial isolates. Based on the research it can be concluded that the solithromycin activity is better than the various antimicrobials recommended for GO therapy and can be used for GO strains that are resistant to cefixime and ceftriaxone (Golparian *et al.*, 2012).

In the Agar Diluting (AD) testing, which was obtained from eight laboratories using a bimodal distribution, Riedel *et al.*, 2015 found that MIC results for eradicating *N. gonorrhoeae* were in the range of 0.06–0.12 µg/mL which is inside the range of Quality Control (QC) which it is proposed to be 0.03–0.25 µg/mL using the Clinical and Laboratory Standards Institute (CLSI) criteria in the bimodal distribution test. All modal MIC values of AD solithromycin were observed from each of the laboratories participating in this study after having been through one dilution doubled 0.12 µg/mL. The AD value obtained was in the range of 0.03–0.25 µg/mL. Meanwhile, the Disk Diffusion (DD) testing which determines the range of medium inhibition zones against *N. gonorrhoeae* from the eight laboratories participating in the study, results between 34–42 mm with a difference of ≤1 mm are still tolerated, covering 95.8% of all zones reported. The accuracy of the Range Finder statistical program was then re-tested to evaluate

the MIC range and zone diameters present in the isolate and obtained a slightly wider DD of 33–43 mm which included 98.5% of all reported zone diameters. Values of AD and DD in this study were then submitted to the CLSI Subcommittee on Antimicrobial Susceptibility Testing in January 2015 and were approved to be the QC range value for agar dilution test results and disk diffusion zone tests (Riedel *et al.*, 2015).

After the research of Mellegol, et al on the activity of solithromycin against *N. gonorrhoeae* at various pHs, it is known that at pH 5.6–7.6, solithromycin exhibits more stable properties in acidic conditions due to exposure to the *N. gonorrhoeae* and intracellular environment compared to azithromycin. This study shows that as a stable anti-gonococcal, solithromycin activity tends to be more potent than azithromycin in acid compartments such as endosomes with pH 6.5 and lysosomes with pH 4 to 5. (Mallegol *et al.*, 2013).

### Clinical Trials of Solithromycin

#### Phase I Clinical Trials and Drug Pharmacokinetics

The pharmacokinetics of the drug was evaluated through phase one clinical trials on 108 healthy individuals aged 19 to 55 years. This study analyzed the pharmacokinetics of administering a single dose of solithromycin, multiple doses, and the effect of food on the bioavailability of the drug. In a single-dose study, 49 people were given a single dose of placebo or solithromycin with 50, 100, 200, 400, 800, 1200, or 1600 mg, whereas, in studies of multiple doses, 35 individuals were given placebo or solithromycin at a dose of 200, 400 or 600 mg for seven consecutive days. Meanwhile, to determine the effect of food, 24 individuals received 400 mg of solithromycin after fasting, 10 hours of fasting or consuming high-fat foods in 30 minutes (Still *et al.*, 2011).

In both single and multiple doses, solithromycin shows an increase in maximum concentration beyond an increase in a dose-proportion manner. Also, the time needed to reach the maximum concentration also increases with increasing doses of solithromycin. Solithromycin shows non-linear pharmacokinetics and can accumulate after multiple doses. Therefore, this study recommends the use of an initial dose which is then followed by a lower follow-up dose (Still *et al.*, 2011).

The oral bioavailability of solithromycin is dose-dependent with a value of 62% (for a single dose of 2 x 200 mg capsule) and has a well absorption from the body (Cempra Inc. & FDA,

2016b; Still *et al.*, 2011). By administering once daily, solithromycin can reach systemic levels with  $T_{max}$  observed 2-4 hours post total dose, so this study shows that solithromycin has broad efficacy and benefits for the management of infection (Cempra Inc. & FDA, 2016a; Golparian *et al.*, 2012). Solithromycin can reach plasma levels of 81% (78–84%) and tissue distribution in high amounts of 400 L (349–554 L) at the administration of 400 mg IV infusion (Cempra Inc. & FDA, 2016a). In both single and multiple doses, solithromycin can also be well tolerated by the body. There are no serious side effects or significant changes in physical examination, vital signs, and laboratory tests. Regarding the influence of food, there is no effect of diet on pharmacokinetics includes bioavailability of solithromycin (Golparian *et al.*, 2012).

Solithromycin is metabolized in the liver through interactions with cytochrome CYP3A4. Solithromycin is an inhibitor of CYP3A4 isoenzymes, so it can inhibit its own metabolism. This explains why accumulation can occur after the administration of solithromycin for several days. Although the main pathway for eliminating solithromycin is through metabolism in the liver, pharmacokinetic studies in patients with mild or moderate liver dysfunction (Child-Pugh grade A or B) have shown a result of cumulative exposure solithromycin in the steady-state (AUC) similar to that observed in subjects standard control with lower outcomes in individuals with severe liver impairment (Child-Pugh class C). These results are associated with a higher body mass index in specific patient groups in the study. No dosage reduction recommendation exists based on this impaired liver function (Jamieson *et al.*, 2015). Multiple metabolites in feces, plasma, and urine are detected after administration of a single 800 mg orally (Cempra Inc. & FDA, 2016a). Solithromycin is also a substrate and inhibitor of P-glycoprotein so that it can increase the concentration of drugs transported by P-glycoprotein (Jamieson *et al.*, 2015).

Solithromycin is mainly excreted in the stool (77%), urine (14%), and excreted without deformation (10%). The terminal half life of this drug is around 8.5 hours (7.2–11.2 hours) after intravenous administration to the healthy subject (Cempra Inc. & FDA, 2016a). In other studies, the pharmacokinetic analysis of solithromycin did not differ significantly between healthy individuals and those with mild to moderate liver damage or kidney failure (Cempra Inc. & FDA, 2016b; Jamieson *et al.*, 2015). This shows that

solithromycin does not require dose adjustments for patients with kidney failure or those with mild chronic liver disease. to moderate, unlike other macrolides. However, dose adjustment is still needed for kidney failure with creatinine clearance <30 mL/min (Cempra Inc. & FDA, 2016b; MacDougall, 2018; Still *et al.*, 2011).

Related to the toxicological aspects of solithromycin, Woodhead *et al.*, 2019 made a study using the Quantitative system toxicology (QST) method using the DILIsym, model to analyze the mechanism of the antibiotic solithromycin in causing DILI. DILIsym is a QST model of liver injury that integrates the results of in vitro toxicity tests with estimated in vivo exposure and known biochemical mechanisms for understanding hepatotoxicity (oxidative stress, mitochondrial dysfunction, and inhibition of bile acid transport) of the drug to be assessed. The study showed that DILI in solithromycin was primarily due to inhibition of the mitochondrial electron transport chain (ETC), which was immediately adaptable by mild liver injury (Woodhead *et al.*, 2019).

#### Phase II Clinical Trials

A total of 59 participants participated in phase II clinical trials for the use of solithromycin in overcoming GO infection. In this study, two different doses of solithromycin are given, namely 1200 mg and 1000 mg. Unlike ceftriaxone which requires parenteral administration, solithromycin can be given by mouth. Results of the study show that solithromycin is 100% effective in eradicating uncomplicated GO in the urogenital, oropharyngeal, and rectum based on culture tests. In addition to using culture, the nucleic acid amplification test (NAAT) is used as a diagnosis of GO and chlamydial infection in genital and extragenital. Very high sensitivity of NAAT causes NAAT to identify additional infections not detected in culture. In this study, the results of the NAAT examination of 87% of participants turned negative after the administration of solithromycin. Nevertheless, NAAT is only supportive of the results of culture examination for solithromycin because NAAT can still show positive results under exposure of non-viable *N. gonorrhoeae* (Hook *et al.*, 2015).

The results of the evaluation of 84 subjects showed overall tolerability of the oral dose of the fluoroketolide regimen and a single dose did not cause cessation of drug use. Common side effects were diarrhea, nausea, and vomiting. However, these side effects occurred after one hour of drug



consumption and were associated with the amount consumed. Diarrhea occurred in 17 (61%) of 28 participants who received a dose of 1200 mg and 13 (42%) of 31 patients who received a dose of 1000 mg. Nausea occurs in 32% of patients who receive a dose of 1200 mg and 26% who receive a dose of 1000 mg while vomiting occurs in 14% and 3% for doses of 1200 mg and 1000 mg respectively (Hook *et al.*, 2015).

A limitation of this study is the absence of isolates that have high resistance to macrolides. However, solithromycin remains effective in treating gonorrhea, including extragenital infections that are difficult to manage such as the pharynx and rectum. Moreover, solithromycin can also overcome *Chlamydia trachomatis* infection and *Mycoplasma genitalium* which is often coexistent with *N. gonorrhoeae* in sexually transmitted infections (Hook *et al.*, 2015).

#### Phase III Clinical Trials

Continuing the previous phase two clinical trial, a randomized phase III clinical study from Chen *et al.*, 2019 has been published to compare a single dose of oral solithromycin 1000 mg daily with urogenital GO standard therapy namely intramuscular ceftriaxone 500 mg plus oral azithromycin 1000 mg single dose evaluated at day seven. The study began on 3 September 2014 until 27 August 2015 with 262 subjects randomly selected to receive therapy. At the beginning of the study, 131 patients received solithromycin therapy and 131 patients received therapy the standard regimen recommendations in Australia, the United Kingdom, and Europe (ceftriaxone plus azithromycin). In this clinical trial, the patient and all investigators were unmasked to the treatment assignment (Chen *et al.*, 2019).

The primary outcome in this study was the cure of the patient based on the eradication rate of *N. gonorrhoeae* expressed in the culture test for the genital site after 7±2 days drug administration which was stated as eradicated, persistent, and indeterminate. On the seventh day of the study, the remaining 252 patients, divided into two research arms: 123 recipients of solithromycin (7 unconfirmed cultures before therapy and 1 getting medication errors) and 129 standard drug recipients (2 unconfirmed cultures before therapy) were analyzed by microbiological intention-to-treat (mITT). Microbiological response to *N. gonorrhoeae* infection on day seven showed an eradication rate of 99 (80%) of 123 patients in the group of solithromycin therapy and 109 (84%) of

129 patients in the group of ceftriaxone plus azithromycin therapy (difference -4.0%, 95% CI -13.6 to 5.5%); therefore solithromycin is not inferior compared to standard treatment. The proportion of patients with GO elimination on the cure test was below than supposed in both therapy groups because of the high number of patients with uncertain healing status (i.e., patients who did not come back to the clinic for the healing assessment test on day 7). This result was also influenced by the persistence of genital GO infection, which occurred only in eight of 123 patients (7%) in the group with genital GO treated with solithromycin. The Phase III randomized clinical trial of solithromycin shows that this new fluoroketolide is not inferior in curing uncomplicated genital GO when compared to ceftriaxone plus azithromycin (Chen *et al.*, 2019).

Secondary results per anatomic site were performed in 212 patients (105 patients in the group treated by solithromycin and 107 patients in the group treated by ceftriaxone plus azithromycin) who were eligible and viable for microbiological isolates to be evaluated with positive culture baseline data for *N. gonorrhoeae* in each anatomic region and were successfully recultured on day 7. Comparison of the solithromycin to ceftriaxone plus azithromycin groups related to eradication rates for genital GO was 97/105 (92%) VS 107/107 (100%), eradication rates for pharyngeal GO were 15/16 (94%) VS 19/19 (100%), and the rectal GO eradication rate is 5/6 (83%) vs. 12/12 (100%). All patients who experienced treatment failure were known to have a solithromycin MIC of 0.06–0.12 µg/mL (still in the susceptible range) which indicates the possibility of involvement of long-acting factors such as inadequate drug exposure and possible inappropriate doses (alternative two-dose regimen) in this treatment failure phenomenon (Chen *et al.*, 2019).

Furthermore, susceptibility tests on 313 viable isolates (248 from genital, 43 from pharyngeal, and 22 from rectal) showed 24.9% of isolates not responsive to ciprofloxacin, 18.5% of isolates resistant to penicillin, and 28.1% isolates not sensitive to tetracycline. Entirely isolates are still susceptible to ceftriaxone, and 99.4% of isolates are sensitive to cefixime. There were 11 (3.51%) isolates considered to be resistant to azithromycin according to the breakpoint criteria of the European Committee on Antimicrobial Susceptibility Testing (MIC >0.5 µg/mL). All studied isolates including those resistant to azithromycin sensitive to solithromycin were

assessed using experimental interpretive MIC criteria (MIC range 0.004-0.25 µg/mL, MIC 50 0.12 µg/mL, MIC 90 0.25 µg/mL). Decreased solithromycin susceptibility here is described as an increment in MIC of *N. gonorrhoeae* isolates four or more times from baseline. The benefit of solithromycin against azithromycin-resistant GO strains in phase three RCTs is challenging to be assessed. Because of the limited number of isolates with decreased susceptibility to azithromycin in a group of patients treated by ceftriaxone plus azithromycin. Further clinical trials are needed to determine the efficacy of solithromycin against GO that is resistant to azithromycin (Chen *et al.*, 2019).

Besides, the safety and tolerability of the drug were assessed from the most common side effects occurring higher in the solithromycin group compared to the ceftriaxone plus azithromycin group i.e. 69/131 (53%) vs. 45/131 (34%). The most common adverse effects in the group of patients treated by solithromycin compared with a group of patients treated by ceftriaxone plus azithromycin were the gastrointestinal side effects of diarrhea 31/131 (24%) vs 20/131 (15%) and nausea 27/131 (21%) vs 15/131 (11%). All of the side effects in the group of patients treated by solithromycin had mild to moderate severity. One patient in a group treated by ceftriaxone plus azithromycin had severe diarrhea. It was thought to be associated with the research drug.

Another concern is liver enzyme abnormalities. Of the patients who had blood examination at the first and seventh day, eight patients had grade 1 liver enzyme abnormalities (1.1- $<$ 2 times increment of alanine aminotransferase from the standard upper limit). Five of 118 patients (4%) treated by solithromycin, and 3 of 116 patients (3%) treated by ceftriaxone plus azithromycin. Three patients had grade 2 enzyme abnormalities (2- $<$ 3-fold increase in the standard upper limit) seen in 2 of 118 patients (2%) in the group treated by solithromycin vs 1 of 116 patients (1%) in a group treated by ceftriaxone plus azithromycin. However, there is no immediate increment in alanine aminotransferase that appeared above three times from the standard upper limit in this trial (Chen *et al.*, 2019). In contrast, several clinical trials of treating community-acquired pneumonia with oral solithromycin (800 mg first day, 400 mg days 2-5) or intravenously (400 mg first day and switching to oral 400 mg per day for seven days) shows an increment of alanine aminotransferase three times

or higher from the standard upper limit. This side effect was observed in 5% and 9% of recipients, respectively (Barrera *et al.*, 2016; File *et al.*, 2016; Llano-Sotelo *et al.*, 2010).

This Phase 3 RCT study has several shortcomings. First, the primary outcome of genital GO eradication is based on an analysis of patients who disappeared during follow-up (with a large enough number) considered to have treatment failure to suggest genital GO eradication was not maximal. In this trial, the second limitation, was that solithromycin was given as monotherapy to prevent difficulties in assessing its efficacy when combined with other antibiotics. Third, in determining the primary outcome, the only confirmatory method used in this trial was culture for microbiological confirmation of baseline GO infection. This trial did not use other techniques like NAAT because it can produce false-positive results. Even though NAAT is assumed to be more sensitive than culture, the larger number of positive genital infection from cultures compared to the number of positive genital infections from NAAT may reflect NAAT inhibition or suboptimal sampling. Culture is also done to confirm the healing of persistently positive NAAT results due to the presence of nonviable gonorrhoeae. Fourth, the abundance of extragenital GO infections among subjects selected into this study is relatively small. It is difficult to assess the efficacy of solithromycin for extragenital GO infection fully. Fifth, the gender proportion in this study has not been balanced. The number of women involved in this study is inadequate because it is dominated by men who have sex with men at the hospital where the sample was taken. Sixth, solithromycin pharmacokinetics data were not obtained from subjects in this experiment (Chen *et al.*, 2019).

In conclusion, this phase 3 RCT results show that oral solithromycin as a single dose of 1000 mg is not proper as a first-line option compared to a combination of ceftriaxone plus azithromycin. However, given the increased resistance to azithromycin and ceftriaxone, which is increasingly widespread, solithromycin can be a new drug to be considered against gonorrhoea. Additional studies are needed to evaluate double dose solithromycin's efficacy in treating genital and extragenital gonorrhoea, including a group of azithromycin-resistant gonorrhoea. Nevertheless, it is necessary to consider the potential for increased gastrointestinal side effects that occur at doses of 1000 mg (Chen *et al.*, 2019).

Table I. A comparison of pharmacology and pharmaceutical aspects of multiple antibiotics in treating of GO

Antibiotics	Range (µg/mL)	MIC <sub>50</sub> (µg/mL)	Effective Doses (mg)	Dosage Type	Bioavailability (%)	Administrative Routes	Side Effects
Solithromycin	0.004–0,25 <sup>a,b</sup>	0.06 <sup>a,b,c</sup>	1000, <sup>d</sup> 1200, <sup>e</sup> or 800 (first day) plus 400 per day for 2-5 days <sup>f</sup>	Single <sup>d</sup> and Daily <sup>f</sup>	62 <sup>g</sup>	Oral <sup>h</sup>	GI disorders <sup>d</sup>
Azithromycin	0.001–>256 <sup>i</sup>	0.5 <sup>i</sup>	1000 <sup>h,j</sup>	Single <sup>h</sup>	34±19 (oral) <sup>k</sup>	Oral, IV <sup>h</sup>	Widen the QT interval <sup>h</sup> Visual impairment, exacerbation of myasthenia gravis <sup>l</sup>
Thelitromycin	0.001–>256 <sup>i</sup>	0.5 <sup>i</sup>	800 <sup>h</sup>	Daily <sup>h</sup>	57 <sup>k</sup>	Oral <sup>h</sup>	Hepatotoxic, GI disorders, widen the QT interval <sup>h</sup>
Erythromycin	0.064–2 <sup>i</sup>	>2 <sup>i</sup>	2.000 (oral) 500 (IV) <sup>h</sup>	Single <sup>em</sup>	35±25 <sup>k</sup>	Oral, IV <sup>h</sup>	Hypersensitivity, GI disorders, hepatotoxic <sup>n</sup>
Cefixime	<0.016–8 <sup>i</sup>	0.032 <sup>i</sup>	400 <sup>h,j</sup>	Single <sup>h</sup>	40.2 <sup>m</sup>	Oral <sup>h</sup>	Hypersensitivity, GI disorders <sup>h</sup>
Ceftriaxone	<0.002–4 <sup>i</sup>	0.016 <sup>i</sup>	250 <sup>h</sup> , 500 <sup>o</sup>	Single <sup>h</sup>	~100 <sup>k</sup>	IM, IV <sup>h</sup>	Hypersensitivity, GI disorders <sup>h</sup>
Ampicillin	<0.016–>256 <sup>i</sup>	1 <sup>i</sup>	500 <sup>h,p</sup>	Single <sup>p</sup>	62 <sup>k</sup>	Oral, IV <sup>h</sup>	Hypersensitivity <sup>h</sup>
Ciprofloxacin	0.002–>32 <sup>i</sup>	4 <sup>i</sup>	500 <sup>h,q</sup>	Single <sup>q</sup>	70 <sup>k</sup>	Oral, IV <sup>h</sup>	Neurotoxic, tendinitis, GI disorders <sup>h</sup>
Spectinomycin	4–>1.024 <sup>i</sup>	16 <sup>i</sup>	2000 <sup>j</sup>	Single <sup>i</sup>	~100 <sup>k</sup>	IM <sup>j</sup>	Hypersensitivity, GI disorders <sup>h</sup>
Tetracycline	0.125–256 <sup>i</sup>	4 <sup>i</sup>	1500 (first day), 500 (daily) <sup>r,s,t</sup>	Single and Daily <sup>r,s,t</sup>	77 <sup>h</sup>	Oral <sup>r,s,t</sup>	Hepatotoxic, deposition in bones and teeth, GI disorders <sup>h</sup>

Notes: GI, Gastrointestinal tract; IM, intramuscular; IV, intravenous. (a) Putnam *et al.*, 2010; (b) Riedel *et al.*, 2015; (c) Olsen *et al.*, 2013; (d) Chen *et al.*, 2019; (e) Still *et al.*, 2011; (f) File *et al.*, 2016; (g) Cempra Inc. & FDA, 2016a; (h) Beauduy *et al.*, 2018; (i) Golparian *et al.*, 2012; (j) WHO, 2016; (k) MacDougall, 2018; (l) Cempra Inc. & FDA, 2016b; (m) Steingrímsson *et al.*, 1994; (n) Faulkner *et al.*, 1988; (o) ASHA, 2019; (p) Ngeow *et al.*, 1991; (q) WHO, 1995; (r) Judson & Rothenberg, 1976; (s) Mayo Clinic & IBM Micromedex, 2020; (t) Drugs.com, 2020.

A summary of research from in vitro to clinical trial study about solithromycin in combating *N. gonorrhoeae* (Table I).

#### Pharmaceutical Aspects of Solithromycin

Current GO infection recommendations in Indonesia is cefixime 400 mg single oral dose (five days if chlamydia co-infected and there are complications) or ceftriaxone 250 mg single dose IM injection or kanamycin 2 grams of single-dose IM injection (Kemenkes RI, 2015; PERDOSKI, 2017). In contrary, GO treatment regimen recommendations in Australia, the United

Kingdom, and Europe is a combination of 500 mg ceftriaxone IM (recommended dose of CDC is 250 mg) plus azithromycin 1000 mg orally as a single dose as was done in phase III clinical trial RCTs (ASHA, 2019; Bignell & Fitzgerald, 2011; WHO, 2016; Workowski & Bolan, 2015). However, the emergence of multi-drug resistant GO is the reason the development of alternative antibiotics must be carried out immediately. From multiple pieces of research, solithromycin has antibacterial activity against GO and potential as an alternative antibiotic in patients who cannot receive ceftriaxone due to allergies or resistance (Golparian *et al.*, 2012).

Table IIa. A Summary of multiple types of research about the antibacterial effect of solithromycin in combating *N. gonorrhoeae*.

	Studies	Findings
Putnam <i>et al.</i> , 2010	<p><b>Study Design</b> Experimental: In vitro study.</p> <p><b>Samples</b> Clinical isolates (SENTRY).</p> <p><b>Number of Samples</b> 34 isolates.</p> <p><b>Intervention</b> Antimicrobial susceptibility tests or MIC based on microdilution technique from the CLSI.</p> <p><b>Findings</b> <b>Range of MIC 0.03–0.25 µg/ml; MIC<sub>50</sub> 0.06 µg/ml; MIC<sub>90</sub> 0.12 µg/ml.</b> Solithromycin was highly active against GO compared to azithromycin (range of MIC 0.06–2 µg/mL; MIC<sub>50</sub> 0.25 µg/mL; MIC<sub>90</sub> 0.5 µg/mL), ceftriaxone (range of MIC ≤0.015–0.25 µg/mL; MIC<sub>50</sub> ≤0.015 µg/mL; MIC<sub>90</sub> 0.12 µg/mL), ciprofloxacin (range of MIC ≤0.002–&gt;32 µg/mL; MIC<sub>50</sub> 0.008 µg/mL; MIC<sub>90</sub> &gt;32 µg/mL), penicillin (range of MIC ≤0.015–64 µg/mL; MIC<sub>50</sub> 1 µg/mL; MIC<sub>90</sub> 32 µg/mL); and tetracycline (range of MIC 0.03–16 µg/mL; MIC<sub>50</sub> 1 µg/mL; MIC<sub>90</sub> 4 µg/mL).</p> <p><b>Explanations</b> Solithromycin has better activity compared with other MLS<sub>B</sub> class agents.</p>	
Golparian <i>et al.</i> , 2012	<p><b>Study Design</b> Experimental: in vitro study.</p> <p><b>Samples</b> Clinical isolates.</p> <p><b>Number of Samples</b> 246 isolates.</p> <p><b>Intervention</b> The MICs were determined by the agar dilution technique recommended by CLSI.</p> <p><b>Findings</b> <b>Range of MIC 0.001–32 µg/ml; MIC<sub>50</sub> 0.125 µg/ml; MIC<sub>90</sub> 0.25 µg/ml.</b> Solithromycin has a substantially higher MIC compare to: azithromycin (range of MIC 0.001–&gt;256 µg/mL; MIC<sub>50</sub> 0.5 µg/mL; MIC<sub>90</sub> 8 µg/mL), telithromycin (range of MIC 0.001–256 µg/mL; MIC<sub>50</sub> 0.25 µg/mL; MIC<sub>90</sub> 1 µg/mL), erythromycin (range of MIC 0.064–2 µg/mL; MIC<sub>50</sub> &gt;2 µg/mL; MIC<sub>90</sub> &gt;2 µg/mL); cefixime (range of MIC &lt;0.016–8 µg/mL; MIC<sub>50</sub> 0.032 µg/mL; MIC<sub>90</sub> 0.25 µg/mL); ceftriaxone (range of MIC 0.002–4 µg/mL; MIC<sub>50</sub> 0.016 µg/mL; MIC<sub>90</sub> 0.125 µg/mL); ampicillin (range of MIC &lt;0.016–&gt;256 µg/mL; MIC<sub>50</sub> 1 µg/mL; MIC<sub>90</sub> 16 µg/mL); ciprofloxacin (range of MIC 0.002–&gt;32 µg/mL; MIC<sub>50</sub> 4 µg/mL; MIC<sub>90</sub> &gt;32 µg/mL); spectinomycin (range of MIC 4–&gt;1,024 µg/mL; MIC<sub>50</sub> 16 µg/mL; MIC<sub>90</sub> 16 µg/mL); and tetracycline (range of MIC 0.125–256 µg/mL; MIC<sub>50</sub> 4 µg/mL; MIC<sub>90</sub> 64 µg/mL). The levels of in vitro resistance of azithromycin 37.8%, erythromycin 94.3%, cefixime 6.5%, ceftriaxone 1.2%, ampicillin 24.4%, ciprofloxacin 64.2%, spectinomycin 2%, and tetracycline 69.5%.</p> <p><b>Explanations</b> The activity of solithromycin was mainly superior to that of other antimicrobials currently or previously recommended for GO treatment. Solithromycin might be an effective treatment option for GO.</p>	
Olsen <i>et al.</i> , 2013	<p><b>Study Design</b> Experimental: in vitro study.</p> <p><b>Samples</b> Consecutive clinical isolates.</p> <p><b>Number of Samples</b> 108 isolates.</p> <p><b>Intervention</b> The MICs were determined by the agar dilution technique recommended by the CLSI and were analysed using the Etest method.</p> <p><b>Findings</b> <b>Range of MIC &lt;0.0016–0.25 µg/ml; MIC<sub>50</sub> 0.064 µg/ml; MIC<sub>90</sub> 0.125 µg/ml.</b> Solithromycin was active against GO compared with gentamicin (range of MIC: 0.032–8 µg/mL; MIC<sub>50</sub> 4 µg/mL; MIC<sub>90</sub> 4 µg/mL), ertapenem (range of MIC 0.002–0.125 µg/mL; MIC<sub>50</sub> 0.012 µg/mL; MIC<sub>90</sub> 0.032 µg/mL). The levels of in vitro resistance of ciprofloxacin 98%, tetracycline 82%, penicillin G 48%, azithromycin 11%, ceftriaxone 5%, cefixime 1%, and spectinomycin 0%.</p> <p><b>Explanation</b> In Vietnam, in vitro resistance to antimicrobials treatment for GO is high. The MICs of three potential future treatment options were low. Research regarding combination therapy and new antimicrobials is crucial for future treatment of GO.</p>	
Mallegol <i>et al.</i> , 2013	<p><b>Study Design</b> Experimental: in vitro study.</p> <p><b>Samples</b> Clinical isolates.</p> <p><b>Number of Samples</b> 196 isolates.</p> <p><b>Intervention</b> The MICs were determined by the agar dilution method according to the CLSI guidelines. The role of pH in MIC determinations using pH-adjusted agar plates (pH range, 5.6–7.6).</p> <p><b>Findings</b> <b>Range of MIC: &lt;0.015–8 µg/ml; MIC<sub>50</sub> 0.0625 µg/ml; MIC<sub>90</sub> 0.125 µg/ml.</b> Compared with azithromycin (Range of MIC 0.031–2,048 µg/ml; MIC<sub>50</sub> 0.25 µg/ml, MIC<sub>90</sub> 0.5 µg/ml). In contrast to azithromycin, solithromycin MICs were not significantly affected by acidic pHs, suggesting it is more stable at lower pH.</p> <p><b>Explanations</b> The intracellular activity of solithromycin with the low MICs to this agent, indicates that solithromycin is potential for GO treatment if clinical trials in development reveal that this drug is safe, especially when multidrug resistance are now emerging.</p>	
Riedel <i>et al.</i> , 2015	<p><b>Study Design</b> Experimental: in vitro multilaboratory : 9 laboratories participated in this study to establish QC ranges.</p> <p><b>Samples</b> Clinical isolates.</p> <p><b>Number of Samples</b> 240 isolates.</p> <p><b>Intervention</b> MIC or AD and DD testing was performed for solithromycin againsts <i>N. gonorrhoeae</i> based on CSLI.</p> <p><b>Findings</b> <b>Range of MIC: 0.03–0.25 µg/ml ; DD 33–43 mm.</b></p> <p><b>Explanations</b> Through this multilaboratory study, CLSI Subcommittee on Antimicrobial Susceptibility Testing approved MIC and DD ranges, which will be important when evaluating solithromycin against clinical isolates of <i>N.gonorrhoeae</i>.</p>	

Table IIb. A Summary of multiple types of research about the antibacterial effect of solithromycin in combating *N. gonorrhoeae*.

	Studies	Findings
Hook <i>et al.</i> , 2015	<b>Study Design</b> <b>Samples</b> <b>Number of Samples</b> <b>Inclusion Criterias</b> <b>Exclusion Criterias</b>	RCT: phase II noncomparative, registered with ClinicalTrials.gov number NCT01591447. Human. 59 participants (28 received 1200 mg of solithromycin and 31 received 1000 mg). Untreated urethral or cervical GO (with identified by microscopic or NAAT testing performed within the preceding 2 weeks, or sexual contact in the past 21 days with a partner diagnosed with GO); and (2) abstain from sexual intercourse or to use condoms until follow-up was complete, and able to swallow 5-6 solithromycin capsules intact. Pregnancy tests were completed for all women, and pregnant women were not enrolled. Complicated or systemic gonococcal infection, concurrent infection requiring antimicrobial therapy; reported allergy to macrolide antibiotics; had condition that could affect oral absorption of the drug; HIV or chronic hepatitis B or C infection; had used systemic or intravaginal antibiotics within the 30 days preceding study; Genital ulcer disease; had an electrocardiographic QTc interval >450 msec in men or >470 msec in women or were taking medications known to prolong the QT interval; significant renal, hepatic, or hematologic impairment; chronically immunosuppressed; recently taken immunosuppressive medications or received a solid organ transplant.
	<b>Intervention</b> <b>Findings</b> <b>Explanations</b>	Single-dose (1200 and 1000 mg) oral solithromycin for treatment of uncomplicated urogenital GO. 46 (78%) participants had positive cultures for GO at the time of enrollment: 24/28 (86%) persons who received 1200 mg, and 22/31 (71%) who received 1000 mg. In addition, 8 participants had positive pharyngeal gonococcal cultures, and 4 had positive rectal cultures. <i>Chlamydia trachomatis</i> and <i>Mycoplasma genitalium</i> coinfections were evaluated. Results were negative at 1 week of follow-up in 9 of 11 (82%) participants positive for <i>C. trachomatis</i> and 7 of 10 (70%) participants positive for <i>M. genitalium</i> . Mild dose-related gastrointestinal side effects (nausea, loose stools, vomiting) were common but did not limit therapy. Oral single-dose 1000 mg and 1200 mg solithromycin was effective for treatment of culture-proven GO at genital, oral, and rectal sites of infection and is a promising new agent for GO treatment.
Chen <i>et al.</i> , 2019	<b>Study Design</b> <b>Samples</b> <b>Number of Samples</b> <b>Inclusion Criterias</b> <b>Exclusion Criterias</b>	RCT: phase III comparative, registered with ClinicalTrials.gov number NCT02210325. Human, (Child, Adult, Older Adult); aged $\geq 15$ years old in USA and Australia. 262 participants (131 solithromycin VS 131 ceftriaxone plus azithromycin). (1) At least one of the following: untreated male with urethral GO; untreated female with cervical GO; and/or urethral (male) or cervical (female) Gram stain demonstrating Gram-negative intracellular diplococci and leukocytes. They within 2 weeks prior to study drug administration (2) Abstain sexual intercourse or use condoms (3) Negative pregnancy test at enrollment.
	<b>Intervention</b> <b>Findings</b> <b>Explanations</b>	(1) Complicated or systemic GO infections; (2) Individuals who have already received antibiotic treatment for their GO; (3) Use of systemic or intravaginal antibiotics within 7 days prior to study drug administration; (4) Woman who are pregnant or nursing; (5) Men with rectal GO and symptoms of proctitis; (6) Intolerance or allergy to macrolide or cephalosporin antibiotics. Patients were randomly assigned (1:1) to receive either solithromycin single 1000 mg dose or standard therapy (ceftriaxone 500 mg IM plus oral azithromycin 1000 mg). An interactive web response system did randomisation. Patients and all researchers were unmasked to treatment assignment. Test of a remedy for GO using culture at day 7 $\pm$ 2 days. <b>Primary outcome:</b> the proportion of patients who were GO eradicated from culture after day 7 with solithromycin compared to standard therapy (80% VS 84%; difference -4.0%, 95% CI -13.6 to 5.5 with -10% margin). <b>Other Outcomes:</b> the frequency of adverse events was higher in the solithromycin group than the standard therapy group (53% VS 34%), such as diarrhoea (24% VS 15%), and nausea (21% VS 11%). Solithromycin as a single 1000 mg dose is not an appropriate option than ceftriaxone plus azithromycin as a first-line treatment for GO. For the possibility of treatment failure in subset of individuals due to insufficient duration of solithromycin therapy at the site of infection then this can be adjusted by increasing the dose. However, any trial with increasing doses needs to consider the potential risk of side effects of gastrointestinal and liver enzyme elevations.

**Notes:** AD, agar dilution; CLSI, Clinical and Laboratory Standards Institute; DD, disk diffusion; GO, gonorrhea; MIC, Minimum Inhibitory Concentration; MLS<sub>B</sub>, macrolide–lincosamide–streptogramin B.

For six decades, solithromycin was primarily produced by semisynthesis by chemically modifying natural products derived from fermentation (Fischbach & Walsh, 2009; Wright *et al.*, 2014). Since erythromycin was discovered, all macrolide class antibiotics, including solithromycin, can be made from chemically modified erythromycin (Seiple *et al.*, 2016). Azithromycin was prepared from erythromycin through four steps, clarithromycin requires six steps (Cempra Inc., 2016), and solithromycin can be produced from erythromycin through sixteen steps of a linear sequence (Putnam *et al.*, 2010).

However, not only through semisynthesis, but the production of macrolide antibiotics is also attempted through the synthesis route by the convergent assembly of the constituent chemical structural components (Seiple *et al.*, 2016).<sup>50</sup>

A clinical pharmaceutical company is trying to develop several solithromycin products for different indications. Solithromycin indicated for community-acquired bacterial pneumonia has passed clinical phase III and the application of a new drug to the U.S. Food and Drug Administration (FDA) has not been approved because it requires some additional information, such as the risk of

hepatotoxicity that is too small to be explored only in 920 patients. The pharmacy company plans to commercialize solithromycin when FDA has been approved it (Cempra Inc., 2016).

Many types of research have discussed the pharmacological studies of multiple antibiotics that are often used for the treatment of gonorrhoea. The comparison of range, MIC, dosage, bioavailability, administration, and side effects of multiple antibiotics in the treatment of *N. gonorrhoeae* (Table II).

## CONCLUSION

Several benefits are obtained by utilizing the potential of solithromycin in the current medical world, especially for the treatment of resistant gonorrhoea. The advantage of solithromycin chemical structure allows the tight binding of the bacterial ribosome; therefore, the efficacy is better than the other macrolides.

Solithromycin is shown to be superior as an anti-gonococcal with a lower MIC than azithromycin as a current drug, more stable, and maintains its potential against isolates at acidic pH. Other advantages of solithromycin include the bioavailability of solithromycin which is not affected by food; well tissue distribution to various types of tissue, such as the lungs, fluid lining the epithelium, and alveolar macrophages; no dose adjustment is needed in patients with chronic liver disease and patients with mild-moderate kidney damage.

However, in phase III clinical trials, it is known that solithromycin has more significant gastrointestinal side effects than current standard therapy, so further research is needed on the side effects of various doses, frequencies, and duration of administration of solithromycin with a higher number of patients and variation to ensure the safety of this new drug. Further studies need to be conducted that discusses the benefits of solithromycin on isolates of GO resistant antibiotics on a large scale. A more effective synthesis procedure to produce solithromycin on a large scale is also needed to make the drug suitable for application in developing countries.

## ACKNOWLEDGMENT

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