Macrolides and associated antibiotics based on similar mechanism of action like lincosamides in malaria

Tiphaine Gaillard¹,²,³, Jérôme Dormoi¹,²,⁴, Marylin Madamet²,⁵,⁶ and Bruno Pradines¹,²,⁴,⁶*

Abstract

Malaria, a parasite vector-borne disease, is one of the biggest health threats in tropical regions, despite the availability of malaria chemoprophylaxis. The emergence and rapid extension of Plasmodium falciparum resistance to various anti-malarial drugs has gradually limited the potential malaria therapeutics available to clinicians. In this context, macrolides and associated antibiotics based on similar mechanism of action like lincosamides constitute an interesting alternative in the treatment of malaria. These molecules, whose action spectrum is similar to that of tetracyclines, are typically administered to children and pregnant women. Recent studies have examined the effects of azithromycin and the lincosamide clindamycin, on isolates from different continents. Azithromycin and clindamycin are effective and well tolerated in the treatment of uncomplicated malaria in combination with quinine. This literature review assesses the roles of macrolides and lincosamides in the prophylaxis and treatment of malaria.

Keywords: Antibiotics, Antimalarial drug, Malaria, Plasmodium falciparum, Macrolides, Lincosamides, Treatment, Resistance

Background

Malaria, a parasite vector-borne disease, is one of the largest health threats in tropical regions, despite the availability of malaria chemoprophylaxis and the use of repellents and insecticide-treated nets [1]. The prophylaxis and chemotherapy of malaria remains a major area of malaria research, and new molecules are constantly being developed prior to the emergence of resistant parasite strains. The use of anti-malarial drugs is conditioned based on the level of resistance of Plasmodium falciparum in endemic areas and the contraindications, clinical tolerance and financial costs of these drugs. Among the compounds potentially used against Plasmodium, antibiotics have been examined in vitro or in vivo.

After tetracyclines, the second family of potential antibiotics in the fight against Plasmodium includes macrolides and macrolide derivatives, a class of compounds with 14-20 membered macrolactone ring. Another class of antibiotics, licosamides whose chemical structure differs from the macrolides, are associated with the macrolides based on similar mechanism of action. Recent studies have examined the effects of the macrolide azithromycin and the lincosamide clindamycin, on isolates from different continents [2–4]. These molecules, whose action spectrum is similar to that of tetracyclines, are typically administered to children and pregnant women [5–11].

This literature review assesses the roles of macrolides and macrolide derivatives in the prophylaxis and treatment of malaria.
activity spectra, are particularly active against the intra-
cellular germs and are currently administered to children
and pregnant women [5–11], conferring a notable advan-
tage compared with tetracyclines. Certain antibiotics of
this family are useful as anti-malarial substances.

The classification of macrolides is based on the num-
ber of carbon links, which distinguishes macrolides
with 14 atoms from 15- or 16-membered macrolides.
The 14-membered erythromycin is the oldest molecule
(1952); all second-generation macrolides: roxithromycin,
clarithromycin and dirithromycin [12] are products of
hemisynthesis and derived from erythromycin. The only
azalide with 15 carbon atoms is azithromycin, produced
through the introduction of a nitrogen atom inserted
into the macrolide nucleus at C10. This modification has
improved the penetration of drugs into macrophages,
fibroblasts and polymorphonuclear neutrophils, facili-
tating increased accumulation within acidified vacuoles
and extending the half-life [4]. It has also improved activ-
ity against Gram-negative bacteria and other pathogens
from parasitic infections [13]. The antibiotics with 16
carbon links are spiramycin and josamycin. Chemical
modifications are constantly being developed to optimize
this family [14].

Lincosamides are antibiotics associated with the mac-
rolides based on a similar action spectrum, although
the structure of these compounds differs. Lincomycin
is a sugar isolated in 1962 from fermentation through
Streptomyces lincolnensis. Substitution of the C7 bear-
ing a hydroxyl function with a chlorine atom generated a
semi-synthetic derivative, such as 7-chloro-7-deoxy-lin-
comycin or clindamycin, with a higher antibiotic activity
and digestive absorption. Clinical trials have shown the
efficacy, safety and practicability of the treatment of P.
falciparum malaria with clindamycin [2].

Pharmacological properties
Macrolides exhibit poor digestive absorption of less than
60 %, and this effect is strongly influenced by food. The
half-life of these drugs is variable, from a short half-life
for erythromycin (2 h) and clarithromycin (4 h) to long
half-life for azithromycin (68 h) [3]. Efforts for develop-
ment of molecules of this family were first employed to
improve pharmacological properties, but not antimicro-
bial activities.

With the exception of cerebrospinal fluid and brain,
macrolides show excellent tissue distribution in tissues,
such as bone and liver. Erythromycin and clarithromy-
cin are highly metabolized in the liver through interac-
tions with cytochrome P450 CYP3A4, which has been
implicated in many drug interactions. The elimination of
macrolide and macrolide derivatives is primarily biliary.
Indeed, liver failure severely disrupts pharmacokinetics.

Concerning azithromycin, mild renal dysfunction and
mild-to-moderate hepatic dysfunction do not signifi-
cantly affect excretion.

Azithromycin is a slightly metabolized molecule, with
37 % bioavailability after oral administration [15]. It is
known to have a large volume of distribution, achieving
high tissue concentrations. It accumulates in hepatic,
renal, pulmonary and splenic tissues and gradually
leaches into the bloodstream over a period of 1 week
[16]. It also accumulates within fibroblasts and phago-
cytic lysosomes; these cells may serve as a reservoir for
slow release of the drug [17]. Compared with older gen-
eration macrolides, it is more stable in acidic media and
has a longer half-life, allowing for once a day [18]. Indeed,
following a standard 500 mg oral dose, peak plasma con-
centrations are attained with a Tmax of 2–4 h; the plasma
half-life of azithromycin is approximately 70 h following
oral formulation [18].

Among lincosamides, clindamycin has a 90 % digestive
absorption. Unlike lincomycin, clindamycin absorption is
not reduced, but only delayed, through food intake. Char-
acterized by slow but thorough anti-malarial activity,
clindamycin presents a remarkably short plasma half-life
(2–4 h) [7]. Lincosamides exhibit good tissue penetra-
tion, and contrary to macrolides, pass the blood–brain
barrier. Clindamycin metabolism occurs in the liver, with
elimination and high bile concentration. In hepatic insuf-
iciency, the half-life can be extended twice and doses
should be reduced accordingly. With respect to the effect
on Plasmodium, clindamycin slowly accumulates in para-
sites [6].

Tolerance
Macrolides are generally well tolerated; moreover,
they exhibit a good safety profile in children and preg-
nant women [14]. The adverse events most frequently
reported are gastrointestinal disorders: nausea, vomit-
ing, and epigastralgia associated with the administered
dose. Other side effects, such as neurosensory in the type
of headache and dizziness disorders, skin allergies and
rare cases of cholestatic hepatitis, have been reported,
but these effects are rare. The “old” molecules typically
present more side effects than the newer molecules.
Macrolides are largely a problem of drug interference,
reflecting the role of cytochrome [19]. Notably, although
the risk of drug interactions is high, the risk of interac-
tions with new molecules is much less important.

Drug interactions are less frequently observed with lin-
cosamides than with macrolides. The oral forms of lin-
cosamides exhibit a more irritative effect (esophagitis)
than the parenteral forms (chemically induced phlebitis).
Systemic reactions, including allergies, skin reactions and
anaphylactic shock, have been reported. Diarrhoea and
digestive disorders primarily occur with the oral forms [2]. Moreover, the appearance of pseudomembranous colitis resulting from Clostridium difficile toxin selection is characterized by profuse watery diarrhea, fever, and occasional bleeding, requiring the discontinuation of treatment [20]. Moreover, rapid intravenous administration might reflect the electrocardiographic changes and even collapse of cardiac arrest observed in response to lincosamide treatments [21]. Haematologic disorders, such as leukopenia, neutropenia, and thrombocytopenia have been reported. Gastrointestinal disorders are frequently reported in patients receiving azithromycin. Doses of azithromycin between 500 and 2000 mg have been used in all trimesters of human pregnancy for the treatment of upper and lower respiratory tract infections, skin diseases, and infections with Chlamydia trachomatis, Mycoplasma and group B streptococci among women allergic to other antibiotics [4]. Nevertheless, azithromycin delays cardiac polarization [21, 22], although preliminary studies concerning the combination of azithromycin with chloroquine for QT prolongation indicate that cardiac instability is not increased under this combination [23].

**Mechanism of antiplasmodial action**

In bacteria, macrolides inhibit the synthesis of cell proteins through binding to the 50S subunit of the ribosome. The inhibition of protein synthesis through the inhibition of transpeptidation explains the postantibiotic effects of this drug, measured after 3–4 h. The macrolide antibacterial spectrum is similar to that of erythromycin. This spectrum is limited to Gram-positive bacteria, and Gram-negative bacilli remain impermeable to these molecules; however, because of the intracellular concentration of these drugs, macrolides are active against intracellular bacteria development [24]. New macrolide compounds, including the azalide azithromycin, and lincosamides present more or less broader antibacterial activity than erythromycin; the lincosamide clindamycin remains of particular interest as therapy for some parasitic infections [13]. Anti-malarial properties occur by targeting the bacterium-derived translational machinery in the relict plastid, apicoplast, present in Plasmodium spp. [14]. This organelle is limited by four membranes and located within parasitic cells; it contains a 35 kb circular DNA allowing [16] replication, RNA transcription and RNA–protein translation [25].

The macrolide antibiotic azithromycin exhibits the best antiplasmodial properties. This molecule targets the 70S ribosomal subunit from the apical complex [16], comprising 50S and 30S subunits. Once fixed, macrolide prevents the synthesis of the polypeptide, which is subsequently prematurely released [4]. The synthesis of a nonfunctional apicoplast, resulting from exposure to azithromycin, is at the origin of the delayed effect of the molecule. Indeed, parasites treated during first 48 h life cycle show non obvious defect from the loss of apicoplast-encoded gene products: organelle morphology, genome replication protein targeting and segregation during cell division remain intact. Likewise, parasites progress normally through the different developmental stages, giving rise to daughter merozoites that successfully reinvade to establish infection of a new host cell. The deleterious effects of antibiotic occur in the second life cycle following antibiotic treatment in which the apicoplast genome fails to replicate [26]. Thus, similar to tetracyclines, the antiplasmodial action of this macrolide is therefore delayed [27, 28]; this phenomenon in which the parasite completes a full cycle before achieving growth inhibition is referred to “delayed death” [29]. Delayed death is a strategy for examining whether an antibiotic acts on the apicoplast, and unlike antiparasitic molecules with immediate effects, the activity of antiparasitic compounds on some functions of the apicoplast is measurable beyond cell division. Several studies have also identified the immediate activity of azithromycin [30–32], well above that of older macrolides. The mechanism responsible for this activity has not been elucidated [14] and clinical studies failed to demonstrate even equivalence of 3-day treatment with azithromycin to other antimalarial drugs [18].

The target of clindamycin has been recently demonstrated in Plasmodium. This drug was originally extrapolated from Toxoplasma gondii, frequently used as a model based on structural similarities [2, 33]. In T. gondii, clindamycin and the three major clindamycin metabolites are fixed to the large subunit ribosomal RNA of the apicoplast [33]. Several studies have shown a lethal effect of clindamycin on potentiated parasites after 72 h of exposure [29], although the antibiotic concentrations were reduced 3–4 factors less than the IC50.

It has also been suggested that parasites exposed to clindamycin divide and invade new host cells, but at this point, the cells are unable to grow and eventually perish. These results, prior to an in-depth study of the apicoplast, revealed the toxicity of clindamycin on a structure involved in the translation of plasmoidal ribosomal RNA into protein [34]. These findings contributed to the antiplasmodial action of clindamycin after 3 days of administration [35]. In 2005, the target of clindamycin was identified [36]. Clindamycin binds the 50S subunit, comprising ribosomal 23S, 5S and ribosomal proteins L4 and L22. The same mode of action was described for azithromycin two years later. Plasmodium falciparum ribosomal protein L4 (PfRP4) has been demonstrated to associate with the nuclear genome-encoded P. falciparum...
ribsomal protein L22 (PfRpl22) and the large subunit rRNA 23S to form the 50S ribosome polypeptide exit tunnel, which could be occupied by azithromycin [16].

Clinical effectiveness
Due to the short half-life of the first generation of macrolides, their use for anti-malarial treatment is limited. The best-studied antimalarial molecules include azithromycin, for which chemical modifications significantly increase the half-life, and clindamycin.

In this section, the clinical trials using azithromycin and those using clindamycin will be successively discussed.

Concerning azithromycin, its antimalarial action was first described in vitro at the beginning of the 90s [17, 37]. At the end of the 90s, the mass distribution of azithromycin through the World Health Organization (WHO) trachoma elimination programme was shown to reduce malarial parasitaemia [38]. Several studies concerning the antiparasitic properties of antibiotics showed the delayed action of the molecule [16, 27, 28]. Only one clinical multicentre study of azithromycin for the treatment of acute uncomplicated P. falciparum malaria was conducted in India on 15 participants. In this study, patients were randomly assigned to groups treated with either azithromycin or chloroquine alone, or azithromycin associated with chloroquine [3]. The resolution of parasitaemia was inadequate with monotherapy with either azithromycin or chloroquine, but combination therapy provided substantially improved clinical and parasitological outcomes. The delayed resolution of parasitaemia and the potential adverse effects that may occur with effective high doses [39] confirmed that this drug was unsuitable for monotherapy treatment by azithromycin. In addition, different associations were tested in vivo (Table 1).

The effects of associations, such as azithromycin–chloroquine and azithromycin–quinine, were additive on sensitive chloroquine strains and synergistic on resistant strains [40]. Other associations were examined, showing effectiveness, associating azithromycin with a rapidly acting schizonticidal compounds, such as lumefantrine or artemisinin [9, 41]. Two in vitro studies [40, 42] suggested that the dihydroartemisinin–azithromycin combination had antagonistic effects and should be avoided. An in vivo study conducted in Thailand [41], a geographic area with high levels of resistance to anti-malarial drugs, showed that azithromycin–artesunate, even when administered only once daily for 3 days, and azithromycin–quinine, administered three times daily, are safe and efficacious combination treatments for uncomplicated falciparum malaria. A randomized controlled trial performed in Tanzanian children did not support the use of azithromycin–artesunate as treatment for malaria; indeed, the 58 % parasitological failure rate observed after day 28 clearly showed that this treatment could not be an appropriate first line treatment for malaria [9]. One clinical trial conducted in Bangladesh performed on 152 patients suggested that this combination was an efficacious and well-tolerated treatment for patients with uncomplicated falciparum malaria compared with the artemether–lumefantrine combination [43]. This study did not consider the re-emergence of parasites in the peripheral blood as a failure of the treatment, although the mean time was 31.5 ± 5 days. Moreover, these authors did not distinguish the study group according to the age of the patients and mixed children and adults for the data integration.

The efficacy of the azithromycin–quinine combination was confirmed in 2006 [44] when 100 % of the patients were cured through high azithromycin regimens (combination of quinine with 1000 mg of azithromycin per day for 5 days or 1500 mg of azithromycin for 3 days).

A longitudinal trial comparing the effects of chloroquine as a monotherapy or in combination with other drugs, including azithromycin, on children with repeated malaria infections in Malawi demonstrated a high efficacy of the repeated administration of different regimens and showed a significantly higher haemoglobin concentration in children in the chloroquine–azithromycin group. This result might reflect the prevention or treatment of bacterial infections [10]. This combination, chloroquine–azithromycin was recently confirmed as highly efficient and well tolerated in African adults [11].

Another combination treatment comprising azithromycin with sulfadoxine–pyrimethamine was tested in pregnant women from Malawi [8]. Sulfadoxine–pyrimethamine has been adopted in many sub-Saharan Africa countries as the drug of choice for intermittent preventive therapy to reduce placental malaria and low-birth weight. The azithromycin–sulfadoxine–pyrimethamine combination might have several advantages: first, although the parasite clearance rate was slow compared with sulfadoxine–pyrimethamine–artesunate, the rate of recrudescence was low and markedly similar between the two groups. Secondly, azithromycin has an adequate safety profile, as this molecule has often been used in pregnant women to treat STIs. In contrast, there has been concern about the use of artemisinin derivatives during the first trimester based on animal studies [45]. Thirdly, azithromycin has a relatively long half-life compared with artesunate. The azithromycin–sulfadoxine–pyrimethamine combination protects the longer-acting drug (sulfadoxine–pyrimethamine) [8], by decreasing the probability of parasites encountering sub-therapeutic drug levels and promoting the development of resistance [46].
Table 1  Clinical trials of azithromycin plus other drug against *P. falciparum* malaria

| Year | Place   | Reference          | Pop | Nb | Azithromycin Dosage/d Route Nb doses/d | Other Drug Drug Dosage/d Route Nb doses/d | Route Days |
|------|---------|--------------------|-----|----|--------------------------------------|------------------------------------------|------------|
| 1996 | Thailand| NaBangchang [78]   | A   | 30 | 500 mg PO 1                            | Art 300 mg 1 PO 3/1                      | 14.8       |
| 2001 | India   | Dunne 2005 [3]     | A   | 64 | 1000 mg PO 2                           | C 600 mg 2 PO 3                         | 90         |
| 2006 | Thailand| Noedl 2006 [41]    | A   | 27 | 1500 mg PO 2                           | A 200 mg 2 PO 3                         | 92         |
|      |         |                    | A   | 16 | 1500 mg PO 2                           | Q 20 mg/kg 2 PO 3                       | 73         |
|      |         |                    | A   | 27 | 1500 mg PO 3                           | Q 30 mg/kg 3 PO 3                       | 92         |
| 2006 | Thailand| Miller 2006 [44]   | A   | 10 | 1000 mg PO 2                           | Q 30 mg/kg 3 PO 3                       | 90         |
|      |         |                    | A   | 20 | 1000 mg PO 3                           | Q 30 mg/kg 3 PO 5                       | 100        |
|      |         |                    | A   | 20 | 1500 mg PO 3                           | Q 30 mg/kg 3 PO 3                       | 100        |
| 2007 | Malawi  | Kalliani 2007 [8]   | P   | 47 | 1000 mg PO 2                           | SP 1500/75 mg 3 PO 2                    | 91         |
| 2008 | Tanzania| Sykes 2009 [9]     | C   | 129| 20 mg/kg PO 1                          | A 4 mg/kg 1 PO 3                       | 42         |
| 2009 | Bangladesh| Thriemer 2010 [43]| A   | 152| 1500 mg PO 1                           | A 200 mg 1 PO 3                         | 95         |
|      |         | or                 | or  | 152| or                                    | or                                       | or         |
|      |         | 30 mg/kg PO 1      | C   | 30 | 30 mg/kg PO 1                          | A 4 mg/kg 1 PO 3                       | 95         |
| 2007–8| Malawi  | Laufer 2012 [10]   | C   | 160| 30 mg/kg PO 1                          | C 10 mg/kg 1 PO 2                       | 99         |
| 2004–6| Africa  | Sagara 2014 [11]   | A   | 227| 1000 mg PO 1                           | C 600 mg 1 PO 3                         | 99         |

Randomized controlled trial

Only trials with adequate dosing, i.e. clindamycin given at least twice daily are mentioned in this table

*Pop population, A adult, C children, P pregnant women

* A artesunate, Ath artemether, C chloroquine, F fosmidomycin, Q quinine, SP sulfadoxine–pyrimethamine
Despite these results, a review from the Cochrane Collaboration [39] concluded that the available evidence suggested that azithromycin was a weak anti-malarial with some appealing safety characteristics, and that azithromycin’s future for the treatment of malaria did not look promising.

Concerning lincosamides, clindamycin is a major antibiotic for the treatment of anaerobic bacterial infections [47]. This drug also presents antimicrobial activity against *Plasmodium*, *Toxoplasma*, *Babesia* and *Pneumocystis* spp. Moreover, clindamycin is the drug of choice for treatment against toxoplasmic chorioretinitis in newborns and one of the treatments recommended in the babesiosis with *Babesia microti* and *B. divergens* [48]. Associated with pyrithamine or primaquine, clindamycin is a treatment of second intention against toxoplasmosis and pneumocystosis [49].

The antiplasmodial indication of clindamycin was managed according to various therapeutic regimens. The effectiveness of clindamycin in monotherapy in this indication was initially reported in 1975 [50]. The WHO repeated this protocol in several studies conducted on different continents, and several sightings have been reported (Table 2), including the effectiveness of clindamycin in monotherapy against malaria. This efficiency is however conditioned through treatment for 5 days, with twice-daily administration, as this molecule acts slowly. Clindamycin is well tolerated, and minor side effects have been reported during treatment. The occurrence of diarrhoea resulting from *Clostridium difficile* has often been reported after treatment with clindamycin, and this side effect might progress to pseudomembranous colitis, as a result of lengthy treatment with antibiotics [51]. The potential problem of severe diarrhoea, observed in patients receiving a prolonged and high dose of clindamycin therapy, is not observed with a low dose and short duration of therapy to treat malaria [52]. The WHO did not ultimately recommend clindamycin treatment when used alone as an anti-malarial treatment, as parasite clearance might be deleterious in cases of significant parasitaemia in fragile subjects (children and pregnant woman) [2]. However, clindamycin is now recommended for pregnant women in the first trimester with uncomplicated malaria, in association with quinine or artemisinin-based combination therapies or oral artesunate for 7 days.

The combination of clindamycin with other rapidly acting drugs is essential for the optimization of treatment.

Table 2 Clinical trials of clindamycin monotherapy against *P. falciparum* malaria

| Study demographic details | Regimen |
|---------------------------|---------|
|                          | Dosage | Form | Nb doses/d | Route | Nb days | Efficacy (%) |
| Study year | Place | Reference | Pop | Nb |  |  |  |  |  |
| 1975 | USA | Clyde, 1975 [50] | A | 3 | 450 mg | Salt | 3 | PO | 3 | 100 |
| 1975 | Thailand | Hall, 1975 [79] | A | 10 | 450 mg | Salt | 3 | PO | 3 | 50 |
| 1981 | Brazil | Alecrim, 1981 [80] | A | 17 | 10 mg/kg | Salt | 2 | IV | 3 | 65 |
| 1981 | Brazil | Alecrim, 1981 [80] | A | 14 | 10 mg/kg | Salt | 2 | IV + PO | 7 | 100 |
| 1982 | Brazil | Alecrim, 1982 [81] | A | 26 | 10 mg/kg | Salt | 2 | IV, PO | 5 | 100 |
| 1982 | Philippines | Rivera, 1982 [82] | A | 24 | 300 mg | Salt | 2 | IV + PO | 7 | 100 |
| 1982 | Philippines | Rivera, 1982 [82] | A | 12 | 600 mg | Salt | 2 | IV + PO | 7 | 100 |
| 1982 | Philippines | Cabrera, 1982 [83] | A | 12 | 10 mg/kg | Salt | 2 | IV + PO | 7 | 100 |
| 1982 | Philippines | Cabrera, 1982 [83] | A | 19 | 20 mg/kg | Salt | 2 | IV | 3 | 89 |
| 1984 | Columbia | Restrepo, 1984 [84] | A | 6 | 20 mg/kg | Salt | 2 | IV | 3 | 100 |
| 1984 | Columbia | Restrepo, 1984 [84] | A | 9 | 10 mg/kg | Salt | 2 | IV + PO | 7 | 100 |
| 1984 | Columbia | Restrepo, 1984 [84] | A | 5 | 20 mg/kg | Salt | 2 | IV | 7 | 100 |
| 1984 | Columbia | Restrepo, 1984 [84] | A | 10 | 20 mg/kg | Salt | 1 | IV | 7 | 100 |
| 1985 | Sudan | El Wakeel, 1985 [85] | A | 20 | 5 mg/kg | Salt | 2 | PO | 5 | 90 |
| 1988 | Brazil | Meira, 1988 [86] | A, C | 129 | 10 mg/kg | Salt | 2 | PO, IV | 5–7 | 97 |
| 1988 | Brazil | Meira, 1988 [86] | A, C | 16 | 10 mg/kg | Salt | 1 | PO, IV | 5–7 | 50 |
| 1988 | Brazil | Meira, 1988 [86] | A, C | 35 | 2.5 mg/kg | Salt | 1 | PO | 5 | 80 |
| 1989 | Brazil | Kremsner, 1988 [20] | A | 35 | 5 mg/kg | Base | 2 | PO | 5 | 100 |
| 1990 | Philippines | Salazar, 1990 [87] | A | 31 | 300 mg | Salt | 2 | PO | 5 | 100 |
| 1990 | Philippines | Salazar, 1990 [87] | A | 10 | 600 mg | Salt | 2 | PO | 5 | 100 |
| 1993 | Gabon | Salazar, 1990 [87] | A | 38 | 5 mg/kg | Base | 2 | PO | 5 | 97 |
| 1994 | East Timor | Oemijati, 1994 [88] | A | 30 | 300 mg | Salt | 2 | PO | 5 | 100 |

A adults, C children
Clinically documented associations essentially involve the combination of clindamycin with quinine or chloroquine. Quinine, showing a rapid onset and short half-life, is the ideal partner. In vitro studies have also shown a synergistic effect when the two molecules are associated [7, 52]. The bioavailability of the two drugs, when co-administered, remains unchanged [53]. A methodology and satisfactory post-treatment follow-up in approximately ten clinical trials with a wide number of patients have been published (Table 3) [2]. The duration of combination therapy remains controversial. While most studies consider that the administration of quinine for at least 7 days and clindamycin for at least 5 days is needed, treatments conducted for 3 days in African studies were effective [52, 54]. Short-duration treatment is justified for obtaining adequate compliance and fear of side effects with quinine. Parasite clearance has been correlated with parasitaemia in children treated for 4 days [55, 56]. In areas of multidrug resistance, such as Thailand, 5–7 days are needed to cure malaria.

The second well-studied combination is clindamycin with chloroquine. *Plasmodium falciparum* is highly resistant to chloroquine in most malarial regions. However, this drug is still widely used and remains a first-line treatment in Africa. The clindamycin–chloroquine combination has been studied in Gabon [52], where chloroquine resistance is markedly high. Clindamycin was administered every 12 h for 3 days, and success rates ranged from 70% in children to 97% in adults, depending on the study [57]. The success rate in children was estimated as 94% with chloroquine administered at a dose of 45 versus 25 mg/kg. Although these findings favour the effectiveness of the combined administration of chloroquine with clindamycin for 3 days, this treatment has not been widely adopted in practice.

Fosmidomycin, a phosphonic acid derivative, is a new anti-malarial drug with a novel mechanism of action that inhibits the synthesis of isoprenoid in *P. falciparum* and suppresses the growth of multidrug-resistant strains in vitro [58]. Studies in Africa evaluating fosmidomycin as a monotherapeutic agent demonstrated that the drug is well tolerated in humans. A randomized, controlled, open-label study was conducted in 2003 in children to evaluate the efficacy and safety of treatment with fosmidomycin combined with clindamycin (30 and 5 mg/kg body weight every 12 h for 5 days, respectively) compared with treatment with either fosmidomycin or clindamycin alone. The combined treatment with the two molecules was superior to that with either agent alone [6].

Since 2010, the WHO advocates artemisinin-based combination therapy (ACT) as the mainstay in combating drug-resistant malaria in Africa [59]. To prevent the emergence of resistant mutants, various drugs have been studied in combination with artemisinin derivatives, according to the underlying principle to combine artemisinins with drugs that have long plasma elimination half-lives. These treatments seems inappropriate for patients from areas with a high rate of malaria transmission because of the increased risk of drug-resistant mutants resulting from prolonged exposure to subtherapeutic levels of the slowly eliminated drug in the combination [7, 60, 61]. In the same way, combination therapy with drugs that have a rapid elimination time reduces the selection of resistant isolates [62]. The difficulty lies in choosing the ideal combination given the pharmacokinetic properties of the molecules used. One clinical trial combining artesunate with clindamycin for the treatment of uncomplicated *P. falciparum* malaria in Gabonese children was reported in 2005 [7]. In this trial, clindamycin was selected based on promising results from animal models, in vitro studies of *P. falciparum* and the use of sequential treatment with artesunate and clindamycin on Brazilian children [63]. An open-labelled, randomized, controlled clinical trial was performed to evaluate the efficacy and tolerance of oral artesunate-clindamycin therapy (2 and 7 mg/kg) administered twice daily for 3 days compared with a standard quinine–clindamycin regimen administered twice daily for 3 days to treat uncomplicated falciparum malaria in 100 children. The results showed that the artesunate–clindamycin combination was consistent with that of quinine–clindamycin with respect to the cure rates (87 versus 94 % at day 28 of follow-up). The decreased fever and parasites clearance were significantly shorter in the artesunate-clindamycin treatment group. Based on the results of this study, clindamycin associated with artemisinin-based combination therapy is a candidate for studies in areas with a high rate of malaria transmission.

Another in vivo study was conducted to evaluate the efficacy and drug interactions of clindamycin in combination with other anti-malarial drugs in populations from endemic areas. Some artemisinin derivatives have been tested on mice, such as the novel semi-synthetic endoperoxide artemisone [64]. This compound is synthesized from dihydroartemisin in a one-step process and in combination with clindamycin, exhibited increased anti-plasmodial activity, improved in vivo half-life, improved oral bioavailability and metabolic stability, and presented tolerance and no neurotoxicity in humans compared with artesunate. Because this drug is a good candidate, clinical studies must be performed to assess the effect of artemisone in combination with other anti-malarials. If macrolides and their derivatives have been considered as good candidates for the treatment of uncomplicated malaria, their pharmacokinetic properties make them inconsistent against malaria in monotherapy [39].
Resistance mechanisms

Resistance to macrolides and lincosamides has been increasingly reported in clinical isolates of Gram-positive bacteria. One aspect of this resistance is the multiplicity of mechanisms and the diversity in phenotypic expression of several of these mechanisms. Bacteria resist macrolides and lincosamides antibiotics in three ways, including target-site modification through methylation or mutation to prevent the binding of the antibiotics to ribosomal targets, which confers broad-spectrum resistance to macrolides and lincosamides, antibiotic efflux, and drug inactivation. However, these last two mechanisms only affect some molecules [65].

Ribosomal methylation remains the most widespread mechanism of resistance. Resistance to erythromycin has been observed in staphylococci since 1956. Biochemical studies indicated that resistance resulted from the methylation of the ribosomal target of the antibiotics, leading to cross-resistance to macrolides, lincosamides and streptogramin B. Subsequently, the MLS\(_2\) phenotype encoded by a variety of \(erm\) (erythromycin ribosome methylease) genes was reported in a large number of microorganisms [66]. \(erm\) proteins facilitate the dimethylation of a single adenine in nascent 23S rRNA, as a part of the large (50S) ribosomal subunit [67]. A wide range of microorganisms, including spirochetes and anaerobes, which express \(Erm\) methylases, are targets for macrolides and lincosamides. The target mutation was first described for \(Escherichia coli\) mutants highly resistant to erythromycin. Mutations in domain V of rRNA were identified in 2001 [68]. Depending on the species, bacteria possess 1 to several \(rrn\) copies, often with each copy carrying the mutation. This mechanism is responsible for the clarithromycin resistance of some \(Mycobacterium avium\), \(Helicobacter pylori\) and \(Treponema pallidum\) strains [65]. Mutations in ribosomal proteins L4 and L22, which confer erythromycin resistance, have been documented for \(Streptococcus pneumoniae\).

The antibiotic efflux is the second mechanism of resistance described for macrolides. In Gram-negative bacteria, chromosomally encoded pumps contribute to intrinsic resistance to hydrophobic compounds, such as macrolides [66, 69]. These pumps often belong to a family comprising proteins with 12 membrane-spanning regions [70]. In Gram-positive organisms, the acquisition of macrolide resistance through active efflux is mediated through two classes of pumps: the ATP-binding-cassette (ABC) transporter superfamily and the major facilitator superfamily (MFS) [71]. The genes encoding these pumps are variable depending on the bacterial genus. The efflux
system is multicomponent in nature, involving plasmidic and chromosomal genes that constitute a fully operational efflux pump with specificity for 14- and 15-membered macrolides and type B streptogramines (the MSB phenotype).

The last mechanism of bacterial resistance is the inactivation of antibiotics. Esterases and phosphotransferases reported in enterobacteria confer resistance to erythromycin and other 14- and 15-membered macrolides, but not to lincosamides. These resistance mechanisms have not been considered of major clinical importance because enterobacteria are not targets for macrolides. Some clinical isolates of S. aureus produce phosphotransferases, but this event remains rare [72–74]. In pathogenic microorganisms, the impact of the three mechanisms is unequal in terms of incidence and clinical implications.

Concerning Plasmodium spp., if prophylactic failures have been observed neither for both the two molecules, in vivo resistance has not been demonstrated nor for clindamycin or azithromycin. However, experimental models of resistant Plasmodium have been developed under selection pressure: strains of P. berghei resistant to clindamycin were described in two studies performed in the 1970s [75, 76]; P. falciparum isolates resistant to azithromycin have been developed later [16], but mechanisms underlying the resistance of Plasmodium against molecules from the MLSB family were not clearly identified. Mutations on A1875 (corresponding to the E. coli A2058 nucleotide in the peptidyltransferase centre of domain V) and A706 (corresponding to the E. coli A754 in domain II) in the P. falciparum apicoplast LSU rRNA (bearing 70% identity to the 235 rRNA [77]) did not confer in vitro resistance to macrolide in P. falciparum as observed in bacterial species [16]. The G1878 mutation, which confers resistance to clindamycin and azithromycin in Toxoplasma gondii [33], remained unchanged in azithromycin-resistant P. falciparum parasites [16]. A mutation was identified at nucleotide position 438 (T438C) after azithromycin-resistance selection. A single point mutation was also identified at codon 76 (G76V) in P. falciparum in azithromycin-resistant parasites [16]. A mutation was identified at nucleotide position 438 (T438C) after azithromycin-resistance selection. A single point mutation was also identified at codon 76 (G76V) in P. falciparum in azithromycin-resistant parasites [16].

Conclusions
The emergence and rapid extension of P. falciparum resistance to principal anti-malarial drugs necessitates the search for new molecules. Macrolides and their derivatives have been considered as good candidates but the design of more effective structural analogues is required, essentially to improve pharmacokinetic properties. The synthesis of single compounds that yields both fast- and slow-acting profiles by targeting different parasite metabolic processes is being developed to achieve effective molecules and mitigate parasite resistance.

Authors’ contributions
All authors read and approved the final manuscript.

Author details
1 Unité de Parasitologie, Département d’Infectiologie de Terrain, Institut de Recherche Biomédicale des Armées, Marseille, France. 2 Unité de Recherche sur les Maladies Infectieuses et Tropicales Emergentes, Aix Marseille Université, UM 63, CNRS 7278, IRD 198, Inserm, 1095 Marseille, France. 3 Fédération des Laboratoires, Hôpital d’Instruction des Armées Saint Anne, Toulon, France. 4 Unité de Parasitologie et d’Entomologie, Département des Maladies Infectieuses, Institut de Recherche Biomédicale des Armées, Brétigny sur Orge, France. 5 Equipe Résidente de Recherche en Infectiologie Tropicale, Institut de Recherche Biomédicale des Armées, Hôpital d’Instruction des Armées, Marseille, France. 6 Centre National de Référence du Paludisme, Marseille, France.

Competing interests
The authors declare that they have no competing interests.

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