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General review

Use of artesunate in non-malarial indications

L'artésunate en dehors du paludisme

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Abstract

Introduction. – Artesunate and other artemisinin derivatives are used in various infectious and non-infectious diseases. We aimed to analyze available data on artesunate and artemisinin derivatives activity in humans and their potential clinical benefits in non-malarial indications.

Material and methods. – Literature review performed on PubMed and the Cochrane Library databases using the PRISMA method. We analyzed studies published in English from January 2008 to August 2017 using the same indicators of drug efficacy.

Results. – We included 19 studies performed in humans (1 meta-analysis, 1 literature review, 4 randomized controlled trials, 3 prospective controlled trials, 3 prospective uncontrolled trials, 2 exploratory phase 1 or 2 trials, 1 case series, and 4 case reports). Artesunate and artemisinin derivatives demonstrated efficacy in the treatment of schistosomiasis in combination with praziquantel ($P=0.003$). Artesunate monotherapy was less effective than praziquantel alone ($P<0.001$) probably because its activity only affects the early stages of *Schistosoma* parasites. Artesunate monotherapy could be interesting as a chemoprophylactic drug against schistosomiasis ($P<0.001$). Findings seem promising but are still controversial in the treatment of multidrug-resistant CMV infections. Studies do not conclude on artesunate and artemisinin derivatives efficacy in the treatment of cervix, breast, colorectal, and lung cancers.

Conclusion. – Artesunate and artemisinin derivatives in combination with praziquantel were effective against schistosomiasis, and could be used as a chemoprophylactic drug alone. They could be interesting as anti-CMV and anti-tumor treatment. Additional trials in humans are required to assess the efficacy of artesunate and artemisinin derivatives in diseases other than malaria.

Keywords: Artesunate; Parasitic diseases; Viral diseases; Cancer

Résumé

Introduction. – L'artésunate et les autres dérivés d'artémisinine sont les traitements de première ligne du paludisme. L'objectif était d'analyser les données disponibles de l'utilisation de l'artésunate et des dérivés d'artémisinine chez l'homme dans d'autres pathologies infectieuses et non infectieuses.

Matériels et méthodes. – Une revue systématique de littérature a été conduite sur PubMed et Cochrane Library, selon une méthodologie PRISMA. Nous avons analysé toutes les études publiées en anglais entre janvier 2008 et août 2017.

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Résultats. – Nous avons inclus 19 études (1 méta-analyse, 1 revue de littérature, 4 essais randomisés contrôlés, 6 essais prospectifs contrôlés et non contrôlés, 2 essais de phase 1 ou 2, 1 série de cas et 4 rapports de cas). L'artésunate et les autres dérivés d'artémisinine ont montré une efficacité dans le traitement de la schistosomose en combinaison avec le praziquantel ($p = 0,003$). L'artésunate en monothérapie est moins efficace que le praziquantel seul ($p < 0,001$). L'artésunate en monothérapie pourrait être utilisé comme agent prophylactique de la schistosomose ($p < 0,001$). Des données d'efficacité, quoique controversées, semblent intéressantes dans le traitement de l'infection à CMV résistant. Les travaux publiés ne permettent pas de conclure à une efficacité dans le cancer du col de l'utérus, du sein, du carcinome colorectal et cancers pulmonaires.

Conclusion. – L'artésunate et autres dérivés d'artémisinine en combinaison avec le praziquantel sont efficaces contre la schistosomose. Ils pourraient être intéressants comme agent anti-CMV et possiblement comme agent antitumoral. Cependant, les travaux publiés ne permettent pas de positionner ces traitements dans d'autres pathologies que le paludisme.

Mots clés : Artésunate ; Infections parasitaires ; Infections virales ; Cancers

1. Introduction

More than 1,600 years ago, Ge Hong (284–346 CE) described the medicinal herb *Artemisia annua* for the treatment of “marsh fever”. In the 1970s, the Chinese project 523 led by Pr Tu Youyou isolated a non-toxic extract of *A. annua*, which induced 100% parasite clearance in animal models of malaria (*Plasmodium berghei* and *P. cynomolgi*) [1]. The active component of this extract, artemisinin, was identified in 1972. Its stereostructure (Sesquiterpene lactones) was identified in 1975. Studies conducted in humans in the 1980–90s led to recommending artemisinin and its derivatives in the first-line treatment of malaria: oral artemisinin-based combination therapy for the treatment of uncomplicated malaria, and parenteral artesunate for the treatment of severe malaria [2–4]. New artemisinin-like ozonides are being investigated as a way to cope with the emergence of artemisinin-resistant *P. falciparum*, and to treat diseases other than malaria. Nonetheless, the mechanisms of action of artesunate and artemisinin derivatives on plasmodial species are not extensively studied and are still controversial [5,6]. The oxidative and metabolic stress triggered by the cleavage of the endoperoxide bond by ferrous heme is the major mechanism of parasite killing.

In in vitro and animal models, artesunate presents broad antiparasitic effects (*Schistosoma* sp., *Fasciola hepatica*, *Babesia* sp., etc.), strong anti-infectious effects (cytomegalovirus, Ebola, etc.), and anti-tumor, anti-inflammatory, anti-oxidant, anti-angiogenesis, and immunomodulatory effects [7,8]. However, artesunate and artemisinin derivative activities in vitro and in humans are different and results must be interpreted cautiously as their half-lives and dosages vary.

The aim of this study was to analyze available data on artesunate and artemisinin derivative activity in humans and their potential clinical benefits in non-malarial indications.

2. Material and methods

We consulted PubMed and the Cochrane Library databases, and used the PRISMA method to conduct this literature review [9].

We included randomized or non-randomized studies published in English from January 2008 to August 2017 performed in humans in controlled or uncontrolled groups. We used the same indicators of drug efficacy between the compared groups. We included meta-analyses and literature reviews, two exploratory phase 1 or 2 trials, case series, and relevant case reports. We used the MeSH terms “artemisinin”, “*Schistosoma*”, “*Fasciola*”, “*Leishmania*”, “cytomegalovirus”, “Ebola virus”, “*Borrelia*”, “lung cancer”, “breast cancer”, “colorectal cancer”, and “cervix cancer”. To introduce these studies performed in humans, we present the most relevant in vitro and animal studies that preceded.

3. Results

3.1. Confirmed mechanisms of action of artesunate and artemisinin derivatives in infectious diseases other than malaria in humans

The most common underlying mechanisms of action of artemisinin derivatives seem to be the oxidative and the metabolic stress as described for *P. falciparum*, responsible for cell damages and the death of the infectious agents [10].

3.1.1. Anti-parasitic action of artemisinin derivatives

Artemisinin derivatives have a wide range of anti-parasitic activity, only demonstrated in in vitro or animal models, against *Trypanosoma* spp., *Toxoplasma gondii*, *F. hepatica*, *Babesia* spp., *Acanthamoeba castellanii*, *Naegleria fowleri*, and *Echinococcus* spp. [7,8,10].

Few studies (Table 1) have been performed in humans to assess the efficacy of artemisinin derivatives against *Schistosoma* spp. ($n=4$), *Leishmania* spp. ($n=1$), and *F. hepatica* ($n=1$).

Schistosomiasis is a helminthic disease affecting more than 200 million people in the tropics as well as travelers. Treatment mainly relies on a single drug, praziquantel, for the chronic stage of the disease. Praziquantel cannot kill schistosomula at the invasive stage of the disease. This results in frequent treatment failures [11]. Artemisinin derivatives were active against schistosomula in in vitro and animal models, and a combination

Table 1

Artesunate and artemisinin derivative activities in human parasitic infections (apart from antimalarial activity).

Activité de l'artésunate et des dérivés d'artémisinine au cours d'infections parasitaires chez l'homme (activité anti-plasmodiale mise à part).

Artesunate action	Type of article	Author, Date	Study design	Results	Limitations
<i>Schistosoma</i> spp.	Meta-analysis	Pérez del Villar et al., 2012 [18]	24 randomized trials included comparing: the therapeutic efficacy of oral artesunate alone, artesunate + sulfadoxine-pyrimethamine, and a combination of artemisinin derivatives + praziquantel against praziquantel alone on schistosomiasis; diagnostic criteria: Kato-Katz thick smears (<i>S. mansoni</i> and <i>S. japonicum</i>) or filtration of urine (<i>S. haematobium</i>); primary outcome measure: parasitological cure (absence of eggs 3 to 8 weeks after treatment); and the preventive efficacy of artesunate and artemether against placebo, administered at 1 or 2-week intervals up to 13 doses in healthy villagers during the high transmission period (2 to 6 months) in endemic areas; diagnostic criteria: please see above; primary outcome measure: infection rate (number of patients infected with <i>Schistosoma</i> spp. against total number of included patients, 3 to 4 weeks after treatment)	Schistosomiasis treatment: => artesunate alone < praziquantel alone; artesunate-sulfadoxine-pyrimethamine < praziquantel alone; artemisinin derivatives + praziquantel > praziquantel alone ; artesunate alone (4 mg/kg/day for 3 days) is less effective than praziquantel (40 mg/kg once) (OR = 0.27 [95% CI 0.13–0.53; $P < 0.001$]); artesunate (4 mg/kg/day for 3 days) + sulfadoxine-pyrimethamine (250 mg/12.5 mg for 3 days or 25 mg for 1 day) is less effective than praziquantel (40 mg/kg/day once) (OR = 0.14 [95% CI 0.02–0.92; $P = 0.04$]); artemisinin (artesunate 4 mg/kg/day for 3 days or artemether 6 mg/kg once) + praziquantel (40 mg/kg once or 3 × 20 mg/kg for 1 day or 6 days) showed a higher cure rate than praziquantel monotherapy with OR = 2.07 (95% CI 1.27–3.36; $P = 0.003$) Schistosomiasis prophylaxis: artesunate or artemether > placebo Artesunate (6 mg/kg once) (RR = 0.11 [95% CI 0.06–0.22; $P < 0.001$]) or artemether (6 mg/kg once) (RR = 0.25 [95% CI 0.16–0.40; $P < 0.001$]) > placebo Artesunate alone is less effective than praziquantel alone Artesunate and praziquantel in combination seem to be more effective than praziquantel alone	Results were compared in various populations Small sample size Lack of studies reporting the efficacy of artemisinin derivatives as prophylactic drugs in <i>S. mansoni</i> and <i>S. haematobium</i> infections (mainly in <i>S. japonicum</i> infections) Studies published in Chinese were excluded whereas many studies have been published in this language on artemisinin derivatives used as prophylaxis in <i>S. japonicum</i> schistosomiasis
	Literature review	Saeed et al., 2016 [13]	3 randomized trials and 3 meta-analyses comparing the efficacy of artemisinin derivatives and praziquantel in the treatment of schistosomiasis were included	Artesunate alone is less effective than praziquantel alone Artesunate and praziquantel in combination seem to be more effective than praziquantel alone	No description of the methodology of this review The authors did not distinguish studies evaluating the efficacy of artesunate as a curative treatment of schistosomiasis from studies evaluating artesunate as a prophylactic treatment
	Randomized controlled trial	Keiser et al., 2014 [19]	To assess the efficacy and tolerability of the following treatments against <i>S. haematobium</i> in school-aged children ($n = 61$) in Ivory Coast: praziquantel (40 mg/kg once); mefloquine (25 mg/kg) combined with praziquantel (40 mg/kg once); mefloquine-artesunate (250mg–100 mg for 3 days) combined with praziquantel (40 mg/kg once) Primary outcome measure: CR and ERR (urine samples collected before, on Days 21–22 and Days 78–79 after the first dosing, and filtrated to detect the eggs)	No statistical difference in efficacy was observed between the three treatment groups at each follow-up (days 21–22 and days 78–79) Day 21–22 post-treatment follow-up: CR = 33% (95% CI 11–55) for praziquantel, 29% (95% CI 8–50) for mefloquine-artesunate-praziquantel, and 26% (95% CI 5–48) for mefloquine-praziquantel; and ERR > 94% for all Day 78–79 post-treatment follow-up: CR = 19% (praziquantel) to 33% (mefloquine-artesunate-praziquantel), and ERR > 90%. Praziquantel monotherapy was the best tolerated treatment (mefloquine-artesunate-praziquantel group: 91% of mild adverse events; mefloquine-praziquantel group: 95% of mild adverse events)	The viability of excreted eggs was not determined. Counts of dead eggs might have been included in the analysis, and the reported cure rates might underestimate the true situation. It is therefore impossible to draw any conclusion

Table 1 (Continued)

Artesunate action	Type of article	Author, Date	Study design	Results	Limitations
	Case report	Martinez-Calle et al., 2013 [22]	A 26-year-old patient presenting with an imported acute schistosomiasis empirically treated as malaria with artesunate (4 mg/kg/day for 1 day then 2 mg/kg/day for 2 days) in Mali. Returning from Mali, the patient presented with eosinophilia, negative urine microscopy, and late seroconversion to <i>S. haematobium</i> (7.5 months). A cystoscopy was performed, and the microscopic examination of the urine identified <i>Schistosomiasis haematobium</i> . Treatment with praziquantel	The patient became asymptomatic without eosinophilia and with a negative urine microscopy, after praziquantel treatment. This case report suggests that artesunate used with a malaria treatment protocol is partially effective during the invasive stage of schistosomiasis	Other studies using artesunate or artemisinin derivatives with various treatment protocols during acute schistosomiasis are needed, as well as studies performed with a larger sample size
<i>Fasciola hepatica</i>	Exploratory phase 2 trial	Keiser et al., 2011 [24]	To assess the efficacy and safety of oral artemether administered at: (i) 6 × 80 mg over 3 consecutive days, (ii) and 3 × 200 mg within 24 hours, in 36 <i>Fasciola</i> -infected individuals in Egypt. Main outcome measure: CR and ERR (multiple Kato-Katz thick smears before and after treatment). In case of treatment failure: triclabendazole	Treatment with artemether 6 × 80 mg: CR 35%; EER 63% Treatment with artemether 3 × 200 mg: CR 6%; EER 0% Artemether was well tolerated. Artemether is not effective to treat fascioliasis Triclabendazole was highly effective (10 mg/kg in 16 patients: CR = 67%, ERR = 94%; and 20 mg/kg in 4 patients: CR = 75%, ERR = 96%) No statistical difference in both groups ($P > 0.05$): Healing rate in the artesunate + sulfamethoxypyrazine/pyrimethamine group: 90%; Healing rate of the placebo group: 85.7% This high healing rate in both arms of the study indicates an important role of the placebo. Artesunate + sulfamethoxypyrazine/pyrimethamine does not prove more effective to treat cutaneous leishmaniasis than placebo	<i>A one-dose treatment of artemether may be insufficient to obtain activity against F. hepatica</i>
<i>Leishmania</i> spp.	Prospective controlled trial	Adam et al., 2009 [25]	Double-blind controlled study comparing artesunate + sulfamethoxypyrazine/pyrimethamine (100 mg artesunate + 250 mg/12.5 mg sulfamethoxypyrazine/pyrimethamine) (n = 20) versus placebo (n = 21) to treat cutaneous leishmaniasis , during 4 consecutive days and repeated 4 times with a free washout interval of 15 days. Outcome measures: clearance or diminution of lesions characterized before treatment and after day 36 and day 72. In case of treatment failure or placebo: pentavalent antimony gluconate		Spontaneous healing of <i>Leishmania</i> spp. is expected and well documented

CR: cure rate; ERR: egg reduction rate.

Bold in tables means important informations or results, to underline the informations or the results and to make easier to read the tables.

of artemisinin derivatives and praziquantel showed synergistic effects [7,8,10,12–14]. In animal models, artemisinin derivatives strongly reduced total worm rates, worm eggs shedding, and egg-caused granuloma in the liver of host animals [13]. Interestingly, artemether, artesunate, and dihydroartemisinin were as active against praziquantel-resistant *S. japonicum* as against the sensitive strain, which shows great promises in the fight against praziquantel resistance [15,16]. The combination of artemether and hemin led to higher worm reduction rates than artemether alone [17]. A recent meta-analysis of studies performed in humans confirmed that:

- artemisinin derivatives used in combination with praziquantel have the potential to increase the cure rates in schistosomiasis treatment, with no significant difference between *S. mansoni*, *S. haematobium*, and *S. japonicum*;
- artesunate alone is less effective than praziquantel alone;
- repeated doses of artemisinin derivatives have a prophylactic effect, significantly reducing the incidence of *Schistosoma japonicum* infections compared with placebo [18].

This prophylactic effect could be explained by the potential efficacy of artemisinin derivatives against schistosomula. Keiser et al. [19] performed a randomized trial and demonstrated that the addition of mefloquine or mefloquine-artesunate does not increase the efficacy of praziquantel alone against chronic *S. haematobium* infection and that praziquantel alone was the best tolerated treatment. Artesunate monotherapy may not be beneficial because its activity only affects the early stages of the parasite. In contrast, praziquantel acts against the mature forms of the parasite, curing 60% to 90% of patients presenting with *S. mansoni* infections and 22% to 83% of patients presenting with *S. haematobium* infections [20,21]. Martinez-Calle et al. [22] reported a case of imported acute schistosomiasis with asymptomatic eosinophilia, with initial negative urine microscopy, empirically treated as malaria with artesunate. The late seroconversion showing *S. haematobium* (7.5 months later) is indicative of a partial effect of artesunate on the course of the disease. However, artesunate was unable to definitely cure the patient. Other studies are required to measure the efficacy of various treatment protocols with artesunate or artemisinin derivatives in acute schistosomiasis.

As artemisinin derivatives in combination with praziquantel seem promising to treat *S. mansoni*, *S. japonicum*, and *S. haematobium* infections additional clinical trials are required to elucidate the effect of these combinations. Artesunate alone as a prophylactic drug should be used with caution as *S. japonicum* resistance to artesunate has already been described in China after 10 years of use in the treatment and prevention of schistosomiasis and as the efficacy on schistosomula is still controversial [22,23].

Fascioliasis is an emerging zoonotic disease of considerable veterinary and public health importance, causing liver and biliary tract infections. Triclabendazole is the only drug available for treatment. In vitro studies and animal models have documented promising fasciocidal properties of artemisinin derivatives [8]. Only one study was performed in humans (phase 2 trial) and

demonstrated that artemether, administered as malaria treatment, showed no or only little effect against fascioliasis, and hence could not represent an alternative to triclabendazole [24]. The role of artemether and other artemisinin derivatives as partner drug in combination chemotherapy remains to be elucidated [24].

Leishmaniasis manifests primarily as cutaneous leishmaniasis, mucocutaneous leishmaniasis, or visceral leishmaniasis, with the latter being fatal if left untreated. Current anti-leishmanial drugs include pentavalent antimonials, amphotericin B, paromomycin, pentamidine, and miltefosine, with toxic effects and emergence of resistance. A large number of in vitro and animal model studies have shown that artemisinin derivatives have an anti-leishmanial activity with limited adverse events [10]. Only one study was performed in humans and failed to demonstrate the efficacy of the combination of artesunate and sulfamethoxypyrazine-pyrimethamine to treat cutaneous leishmaniasis compared with placebo, as described in Table 1 [25].

3.1.2. Antiviral activity of artesunate and artemisinin derivatives

Artemisinin derivatives present a wide range of antiviral activities, proven in in vitro or animal models, against cytomegalovirus (CMV), hepatitis B virus, hepatitis C virus, HIV 1, Epstein-Barr virus, herpes simplex viruses 1 and 2 (HSV1 and HSV2), human herpes virus 6, polyomavirus, and Ebola virus [7,8,26].

Few studies have been performed in humans to assess the efficacy of artesunate against HSV2 ($n = 1$), CMV ($n = 5$), and Ebola virus ($n = 1$) (Table 2).

One case report described an HSV2 infection resistant to aciclovir, penciclovir, and foscarnet in an immunocompromised patient who fully recovered after 30 days of oral artesunate (100 mg per day) [27].

CMV is a major cause of disease in immunocompromised individuals, including patients presenting with AIDS and transplant recipients. It is also a common cause of congenital infection. Artesunate has proved active against CMV in in vitro and animal models [8,26,28]. Such studies demonstrated the efficacy of artesunate against CMV, even against ganciclovir-resistant CMV strains [8,28]. The in vitro combination of artesunate and conventional anti-CMV drugs seems to be an interesting strategy for the treatment of CMV infections to reduce toxicity and drug resistance development [29]. Moreover, artesunate does not target the viral DNA polymerase of CMV and its mechanisms of action rely on the inhibition of the central regulatory processes of CMV-infected cells (such as activation pathways dependent on NF- κ B or Sp1). It thus interferes with critical host-cell type and metabolism requirements for CMV replication [26]. This is interesting as artesunate presents a lower toxicity than conventional anti-CMV drugs. Very few case reports and case series describing the clinical effects of artesunate on CMV infection are available, and they reported controversial results [30–33]. Some case reports of patients presenting with multidrug-resistant CMV infection demonstrated the efficacy of oral artesunate (100 mg per day) for at least 30 days [30,31,33]. Two prospective controlled trials

Table 2

Artesunate and artemisinin derivative activities in human viral and bacterial infections.

Activité de l'artésunate et des dérivés d'artémisinine au cours des infections virales et bactériennes chez l'homme.

Artesunate action	Type of article	Author, Date	Study design	Results	Limitations
Antiviral HSV2	Case report	Sellar et al., 2012 [27]	An 18-year-old woman developed an HSV2 infection 15 days after a stem cell transplant (perineal and labial ulcerations; PCR testing of swabs and in the serum: HSV-2+). Multidrug-resistant HSV2 was identified after transient responses to valaciclovir, foscarnet, and cidofovir. As the lesions did not disappear, oral artesunate (100 mg/day) was introduced	Within 4 days of artesunate initiation, the lesions were less painful. After completing 30 days of artesunate treatment: complete resolution of the lesions and negative HSV2 PCR on a perineal swab for the first time since the lesions had appeared 9 months before. A second and third reactivation of HSV2 also rapidly responded to oral artesunate (100 mg/day) with a resolution of the lesions and a negative HSV2 PCR. No toxicity problem was observed with artesunate	Confounding factors: concomitant reduction in immunosuppression and a gradual rise in lymphocyte count Unknown mechanisms of action of artesunate in HSV2 infections Artesunate (100 mg/day) administered for 30 days may result in adverse events such as anemia or neutropenia. Further studies are required to conclude on the efficacy and safety of artesunate in HSV2 infections
CMV	Prospective controlled trial	Barger-Kamate et al., 2016 [34]	To assess the efficacy of artemether-lumefantrine (n = 164, treated for malaria) on CMV shedding in urines compared with no treatment (n = 143) in Malian children presenting with fever. Urine samples were collected at Day 0, Day 3, and Day 14. CMV DNA was quantified using real-time PCR	Day 0 endpoint: 81/164 case patients (49%) and 88/143 controls (62%) shed CMV. Day 0 and day 3 viral loads were similar. Day 14 endpoint: median viral load of case patients < controls (360 versus 720 copies/mL or 2.56 versus 2.86 log ¹⁰), P=0.059. Day 0 in high viral shedders (> 1,000 copies/mL) showed significantly lower median viral load at Day 14 in case patients (490 copies/mL, 2.69 log ¹⁰) than in controls (1,200 copies/mL, 3.08 log ¹⁰), P=0.045. => Among high virus shedders artemether-lumefantrine decreased urine viral load, but the effect was not observed when analysis of both high and low shedders was performed	No control group of children shedding CMV without malaria treated with artemether-lumefantrine High rates of CMV shedding in this population, questioning the reliability of the diagnostic methods
	Randomized controlled trial	Gantt et al., 2013 [35]	Quantitative CMV DNA PCR performed on dried blood spots collected from 494 Ugandan children, who were randomized either to artesunate + amodiaquine or sulfadoxine-pyrimethamine + amodiaquine for acute malaria infection	CMV detection: in 11.4% of children prior to treatment and 10.7% 3 days later (P=0.70). Average quantity of CMV: 0.30 log ¹⁰ copies/million cells, and higher on Day 3 than Day 0 (95% CI 0.01–0.58, P=0.041). No measurable difference in either the frequency or quantity of CMV detected in blood between both arms	Only 3 days of artesunate combined with amodiaquine whereas with the conventional treatment with ganciclovir the viral load of CMV in blood decreases slowly in transplant patients (<0.5 log ¹⁰ copies/mL) Maybe longer courses and higher doses than those used for malaria are required to decrease CMV viremia
	Prospective uncontrolled pilot study	Wolf et al., 2011 [33]	6 stem cell transplant recipients received preemptive artesunate (200 mg × 2/day for 1 day, followed by 100 mg/day for 28 days) as a compassionate treatment for multidrug-resistant CMV infection . Viral kinetics following initiation of artesunate was calculated. Artesunate was discontinued upon lack of clear virological response (defined as viral load increase or decrease by <0.5 log DNA copies/ml) on days 7, 14, and 21	Two patients demonstrated a rapid 0.8–2.1 log viral load decline by Day 7, with a viral decay half-live of 0.9–1.9 days Four patients demonstrated a continuous viral growth during treatment No adverse events were observed in treatment courses of up to 28 days A divergent antiviral efficacy was revealed, ranging from 43% to 90%, which appeared to be primarily dependent on the virus baseline growth dynamics	Further dose escalation studies are required to examine the role of artesunate in the treatment of CMV infection in transplant recipients The small number of patients and the early discontinuation of artesunate in 4/6 patients do not enable to conclude on artesunate antiviral efficacy in heavily immunosuppressed patients

Table 2 (Continued)

Artesunate action	Type of article	Author, Date	Study design	Results	Limitations
	Case series	Germi et al., 2014 [31]	CMV strains resistant to ganciclovir, cidofovir, and/or foscarnet were genotypically and phenotypically characterized in two hematopoietic stem cell transplant recipients and three solid-organ transplant recipients presenting with CMV disease. Oral artesunate (80 mg to 200 mg/day) was administered for 1 to 7 months	Artesunate led to a favorable virological and clinical response in three patients presenting with mild CMV diseases (fever and neutropenia) but was ineffective in two patients with fatal CMV diseases with lung involvement in spite of a decrease in the CMV DNA load in blood and broncho-alveolar fluid. No severe adverse event was observed. Artesunate may be useful in treating mild CMV disease without organ involvement due to multidrug-resistant CMV strains	Unknown exact mechanisms of action of artesunate in CMV infections. It is also known that there is a low level of artesunate in animal lung tissues - Artesunate dosage of 100 mg/day in the long term may result in severe adverse events such as anemia and neutropenia. Further studies are required to conclude on the efficacy and safety of artesunate in CMV infections
	Case report	Shapira et al., 2008 [30]	A 12-year-old boy presented with a CMV viremia after a stem cell transplantation . Ineffective treatment with foscarnet (60 mg/kg × 3/day). Then ineffective combination with cidofovir (5 mg/kg/week), ganciclovir (5 mg/kg × 2/day) and IV immunoglobulins. Then treatment with IV artesunate (100 mg/day) for 30 days initially administered as a compassionate treatment.	Rapid reduction in viral load (1.7–2.1 log reduction at day 7, viral half-life of 0.9–1.9 days) and improved hematopoiesis One recurrent episode of CMV viremia and CMV retinitis on day 346 treated with IV artesunate and intravitreal ganciclovir, allowing for a sustained virological response (day 665)	Unknown exact mechanisms of action of artesunate in CMV infections Artesunate dosage of 100 mg/day administered for 30 days may result in severe adverse events such as anemia or neutropenia. Further studies are required to conclude on the efficacy and safety of artesunate in CMV infections
		Stuelher et al., 2015 [32]	Multidrug-resistant CMV emerged after transient responses to ganciclovir, foscarnet, and cidofovir in a CMV-seropositive recipient who underwent allogeneic hematopoietic stem cell transplantation from a CMV-seronegative donor. Treatment with leflunomide (20 mg × 2/day) failed. Experimental treatment with artesunate (100 mg × 2/day) + maribavir (400 mg × 2/day)	The viral load declined from 75,000 IU/mL (4.88 log¹⁰ IU/mL) to 8,500 IU/mL (3.93 log¹⁰ IU/mL) within 14 days. Artesunate was withdrawn 2 weeks after initiation because of orthostatic hypotension. Experimental treatment using artesunate failed because of adverse events Re-transplantation from a CMV-seropositive donor supported by adoptive transfer of pp65-specific T-cells and maribavir was followed by long-lasting suppression	The early discontinuation of artesunate does not enable to conclude on artesunate antiviral efficacy Artesunate dosage of 200 mg/day may result in severe adverse events such as anemia or neutropenia. Further studies are required to conclude on the efficacy and safety of artesunate in CMV infections
Ebola virus	Prospective controlled trial	Gignoux et al., 2016 [36]	To estimate the risk ratio (RR) for death among patients presenting with confirmed Ebola virus disease (<i>n</i> = 382) who were prescribed artesunate-amodiaquine (<i>n</i> = 71) , as compared with those who were prescribed artemether-lumefantrine (<i>n</i> = 194) and those who were not prescribed any antimalarial drug (<i>n</i> = 117)	125/194 patients (64.4%) in the artemether-lumefantrine group died versus 36/71 patients (50.7%) in the artesunate-amodiaquine group. In adjusted analyses, the artesunate-amodiaquine group had a 31% lower risk of death than the artemether-lumefantrine group (RR 0.69; 95% CI, 0.54–0.89), with a stronger effect observed among patients without malaria	Amodiaquine is active against Ebola virus: these results do not enable to conclude on the efficacy of artesunate against Ebola virus disease Artemether-lumefantrine may increase the risk of death in patients presenting with Ebola virus disease (e.g. contraindication in patients with known hypokalemia)
Antibacterial <i>Borrelia burgdorferi s.l.</i>	Uncontrolled prospective pilot trial	Puri et al., 2017 [45]	7 patients with Lyme borreliosis included to assess the efficacy of artesunate (20 mg × 4/day) in combination with ceftriaxone on short-term memory outcomes . Diagnostic criteria: serology (not specified); treatment evaluation: self-report questionnaire on short-term memory	No significant reduction in the severity of short-term memory difficulties (<i>P</i> ≈ 0.08) in patients treated with artesunate + ceftriaxone	Stages and symptoms of Lyme borreliosis, serology, self-report questionnaire, and duration of treatment not mentioned Other concomitant medications not evaluated

HSV2: type 2 Herpes Simplex Virus; CMV: cytomegalovirus; IV: intravenous; RR: Risk ratio; AE: Adverse events.

Bold in tables means important informations or results, to underline the informations or the results and to make easier to read the tables.

were performed. The first trial reported a lower median viral load of CMV in the urine of patients treated for malaria with artemether-lumefantrine than in the urine of those who did not receive antimalarial treatment [34]. The second trial did not report any difference in the blood viral load of CMV in children treated with standard three-day artesunate-amodiaquine or sulfadoxine/pyrimethamine-amodiaquine [35]. Longer treatment courses and/or higher doses of artesunate than those routinely used for malaria may be required for an effective treatment of CMV infection. Further studies are required to assess the efficacy of artesunate against CMV in humans.

During the last Ebola epidemics (2014–2016), antimalarials were systematically prescribed to all patients presenting with Ebola virus disease. One study of 382 patients demonstrated that the artemether-amodiaquine group had a 31% lower risk of death than the artemether-lumefantrine group (RR 0.69; 95% CI 0.54–0.89) [36]. Nonetheless, amodiaquine is known for its anti-Ebola virus activity. This study therefore does not prove the activity of artemether against Ebola virus.

3.1.3. Antifungal activity of artesunate and artemisinin derivatives

No study in humans has been performed. Artemisinin derivatives showed in vitro activity against *Cryptococcus neoformans*, *Candida albicans*, and *Aspergillus fumigatus* [7,8]. A synergistic effect was reported in combination with miconazole for *C. albicans* and with itraconazole for *A. fumigatus* [37,38].

3.1.4. Antibacterial activity of artesunate and artemisinin derivatives

Several studies conducted in animal models reported that artesunate could enhance the anti-MRSA (methicillin-resistant *Staphylococcus aureus*) and the anti-*E. coli* activity of beta-lactams by inhibiting the release of pro-inflammatory cytokines and by increasing antibiotic accumulation in the bacteria via inhibition of the multidrug efflux pump system AcrAB-TolC [39–42]. We did not find any study performed in humans.

An in vitro study demonstrated the activity of artemisinin against in vitro amoxicillin-induced round bodies of *Borrelia burgdorferi* but artemisinin presented high minimum inhibitory concentrations (MICs) in active forms of *Borrelia* [43]. Moreover, these round forms of *Borrelia* are only observed in vitro and not in vivo [44]. In Lyme borreliosis, a non-comparative pilot study conducted in seven patients did not report any significant reduction in the severity of short-term memory difficulties ($P \simeq 0.08$) in patients treated with artesunate and ceftriaxone [45]. The diagnostic criteria of borreliosis, the disease stage and symptoms, and the self-report questionnaire were not reported. Moreover, these patients received many other medications poorly evaluated in clinical trials (N-acetylcysteine, cholestyramine, broccoli extract, artichoke extract, etc.) that represent confounding factors to evaluate artesunate efficacy. Therefore, this study does not enable to conclude on the efficacy of artemisinin in human Lyme borreliosis.

3.2. Mechanisms of action of artesunate and artemisinin derivatives in non-infectious diseases

3.2.1. Anti-tumor activity of artesunate and artemisinin derivatives

The in vitro activity of artesunate against tumor cells was confirmed by animal studies of glioblastoma, brain tumor, pituitary macroadenoma, esophageal cancer, breast cancer, colorectal cancer, lung cancer, cervix carcinoma, melanoma, pancreatic cancer, hepatocellular carcinoma, prostate cancer, ovarian cancer, and leukemia [7,8,46–51]. Its mechanisms of action are based on the cleavage of the endoperoxide bridge and its subsequent oxidative stress responsible for:

- the formation of free radicals;
- a cycle cell arrest in phase G0-G1;
- DNA damages;
- NF-kB signaling;
- apoptosis, autophagy, ferroptosis;
- angiogenesis inhibition;
- an effect on signal transduction pathways (e.g. TCTP which regulates cell cycle transition, apoptosis, calcium homeostasis, and cytoskeleton) [52].

The role of iron in artemisinin derivative activity has already been described above and is crucial for tumor cells that express significantly more transferrin receptor on their cell surface than normal cells [52–54]. It explains why artemisinin derivatives preferentially kill tumor cells rather than normal cells. It also indicates that ferrous iron and transferrin might boost artemisinin derivative cytotoxicity in a tumor-specific manner. For example, ferrous glycine sulfate enhanced artemisinin-induced cytotoxicity in most tumors, including cisplatin-resistant neck tumor, but adverse events were described [53,54]. Moreover, specific cytotoxicity of artemisinin towards colorectal cancer (CRC) cells can be enhanced with the addition of aminolevulinic acid (ALA), a clinically used heme synthesis precursor, to increase heme levels. This novel artemisinin/ALA combination therapy proved to be more effective than artemisinin monotherapy in a mouse xenograft CRC model [49]. To our knowledge, no study conducted in humans and assessing these combinations has been published.

Few studies have been performed in patients presenting with neoplastic diseases. Several case studies reported the efficacy of artemisinin derivatives administered as compassionate treatments for uveal melanoma, glioblastoma, prostatic cancer, hepatocellular carcinoma, breast cancer, and laryngeal squamous cell carcinoma [55]. Only four controlled trials [56–59] were conducted in lung, colorectal, breast, and cervix cancers (Table 3).

Zhang et al. [56] performed a randomized controlled trial and reported that artesunate could be used for the treatment of non-small cell lung cancer (NSCLC) in combination with vinorelbine and cisplatin as the disease control rate was higher than with standard chemotherapy alone, and the time to progression was longer. As the article was written in Chinese, we could not

Table 3

Artesunate and artemisinin derivative activities in human cancers.

Activité de l'artésunate et des dérivés d'artémisinine au cours des cancers chez l'homme.

Artesunate action	Type of article	Author, Date	Study design	Results	Limitations
Lung cancer	Randomized controlled trial	Zhang et al., 2008 [56]	120 case patients of advanced NSCLC randomly divided into simple chemotherapy group (control group, n = 60 , vinorelbine (25 mg/m ² IV, day 1 and day 8) and cisplatin (25 mg/m ² IV, from Day 2 to Day 4) and artesunate-chemotherapy group (trial group, n = 60, same chemotherapy and artesunate (120 mg/day IV, from day 1 to day 8). Primary outcomes: short-term survival rate, DCR, TTP, MST, 1-year survival rate, toxicity, and safety	No significant differences in the short-term survival rate, MST and 1-year survival rate between the trial group and the control group (P > 0.05). DCR of the trial group (88.2%) > control group (72.7%) (P < 0.05). TTP of the trial group (24 weeks) longer than the control group (20 weeks) (P < 0.05). No significant difference observed in toxicity between both groups, such as myelosuppression and digestion reaction (P > 0.05)	Article in Chinese. Abstract available in English. No details on the methodology. Results should be interpreted with caution. Impossible to draw any conclusion from this study
Breast cancer	Uncontrolled phase I trial	Von Hagens et al., 2017 [58]	Prospective, monocentric, open, uncontrolled, phase I dose-finding study (optimal daily dose and safety of prolonged treatment) in patients (n = 23) presenting with advanced breast cancer : 100, 150, and 200 mg oral artesunate/day as add-on therapy along with different guideline-based standard therapies Primary endpoints: type, number, intensity, and severity of DL-AEs possibly, probably, or certainly related to artesunate (NCI CTC-AE Version 3.0.). Secondary endpoints: response rates and clinical benefit (routine results, CA15-3, liver ultrasound)	Trial period of 4 ± 1 weeks. Three patients experienced 6 DL-AEs (leukopenia, neutropenia, asthenia, anemia) possibly related to artesunate. Up to 200 mg/day (2.2–3.9 mg/kg/day) of oral artesunate were safe and well tolerated Response assessment was not possible in eight patients (dose 100 mg and 200 mg). Stable disease, considered as a clinical benefit, was observed in 10 patients (dose 150 mg and 200 mg). The other assessable patients (n = 5) experienced progression	Observational descriptive analysis in a very small number of patients; difficult to conclude on artesunate efficacy in breast cancer
Colorectal cancer	Randomized controlled trial	Krishna et al. 2015 [57]	Monocentric, randomized, double-blind, placebo-controlled trial to compare the efficacy of artesunate (200 mg/day for 14 days; n = 12) with placebo (n = 11) in patients planned for curative resection of biopsy-confirmed single primary site CRC Primary outcome measure: proportion of tumor cells undergoing apoptosis (significant if > 7% showed Tunel staining). Secondary outcomes: VEGF, EGFR, c-Myc, CD31, Ki67, and p53, and clinical responses	20 patients (artesunate = 9, placebo = 11) completed the trial per protocol. Apoptosis in > 7% of cells in artesunate group: 67%; in placebo group: 55% (P > 0.05). Using Bayesian analysis, the probabilities of an artesunate treatment effect reducing Ki67 and increasing CD31 expression were 0.89 and 0.79, respectively. During a median follow up of 42 months, 1 patient in the artesunate and 6 patients in the placebo group developed recurrent CRC Artenimol-R induced clinical remission in 2 patients for > 6 months with a resolution of symptoms within 7 days. No adverse event of grade 3 or 4 occurred. The expression of p53, EGFR, and antigen Ki-67 (cellular marker of proliferation), and the number of blood vessels stained by the CD31 antibody decreased, whereas the expression of transferrin receptor protein 1 (CD71) increased	Small sample size Variability in quantitative immuno-histochemical markers No informative pre-defined primary endpoint (proportion of patients with > 7% Tunel positive staining of tumor cells) after artesunate treatment: because of an unexpectedly high proportion (55%) of placebo recipients? Only interpretable secondary endpoints
Cervix carcinoma	Uncontrolled prospective trial	Jansen et al., 2011 [59]	Open-label monocentric study to assess the safety and the potential clinical benefit of artemimol-R (hemi-succinate ester of artemimol) (100 mg to 200 mg/day) in advanced cervix carcinoma (n = 10 patients) . Primary outcomes: clinical symptoms, vaginal discharge and pain, and tumor markers (immunohistochemistry on biopsies). Adverse events recorded	Artemimol-R induced clinical remission in 2 patients for > 6 months with a resolution of symptoms within 7 days. No adverse event of grade 3 or 4 occurred. The expression of p53, EGFR, and antigen Ki-67 (cellular marker of proliferation), and the number of blood vessels stained by the CD31 antibody decreased, whereas the expression of transferrin receptor protein 1 (CD71) increased	Very small sample size Variability in quantitative immuno-histochemical markers Difficult to conclude on the efficacy of artesunate in cervix carcinoma

VEGF: vascular endothelial growth factor; IV: intravenous; DCR: disease control rate, TTP: time to progression, MST: mean survival time; DL-AEs: Dose-Limiting-Adverse Events, defined as clinically relevant adverse events with a grade C3, at least possibly related to artemisinin; EGFR: Epidermal growth factor receptor; c-Myc: c-Myelocytosis; CMV: Cytomegalovirus; NSCLC: Non-small-cell lung cancer; CRC: Colorectal cancer.

Bold in tables means important informations or results, to underline the informations or the results and to make easier to read the tables.

analyze it in detail and it is impossible to draw a conclusion from these results.

Krishna et al. [57] performed a randomized placebo-controlled trial and demonstrated that artesunate had anti-proliferative properties in colorectal cancer (reduction of the expression of Ki67, which is an important prognostic tumor marker in colorectal cancer). However, they could not conclude on the clinical efficacy as their first endpoint could not be interpreted. Artesunate was well tolerated.

Von Hagens et al. [58] performed a prospective, monocentric, open, uncontrolled, phase I, dose-finding study (optimal daily dose and safety of prolonged treatment) in patients ($n = 23$) presenting with advanced breast cancer. Oral artesunate was safe and well tolerated up to 200 mg/day. Response assessment could not be performed for eight patients. Stable disease, considered as a clinical benefit, was however observed in 10 patients (150 mg and 200 mg). Progression was observed in the remaining assessable patients ($n = 5$).

Jansen et al. [59] reported an improvement in clinical symptoms (2/10 patients) and the good tolerability of Artenimol-R in 10 patients presenting with advanced carcinoma of the uterine cervix.

These trials do not enable to conclude on artesunate efficacy in lung, colorectal, breast, and cervix cancers due to methodological limitations (small samples, outcomes, etc.).

3.2.2. Anti-inflammatory effect of artesunate and artemisinin derivatives

Anti-inflammation is the third main effect of artemisinin derivatives. They are able to regulate innate and adaptive immunity in vitro and in vivo [60]. They significantly reduce the phagocytosis of macrophages and the in vivo phagocytic index, and they inhibit TNF α production from macrophages (suppression of nuclear translocation of NF- κ B) [39–42]. Besides suppressing pro-inflammatory cytokine production, artemisinin derivatives could also induce the anti-inflammatory cytokine production, such as IL-10 [61]. Artemisinin derivatives can suppress T cell activation and IL-2 production both in vitro and in vivo [62]. This latter study revealed that artemisinin derivatives (precisely SM934) could exhibit extensive protective effects in chronic inflammation conditions such as clinically effective corticosteroids. Several animal studies demonstrated a good effect on autoimmune diseases (arthritis, dermatitis, hepatic and pulmonary fibrosis, myasthenia gravis, colitis, encephalomyelitis, systemic lupus erythematosus, etc.), allergic diseases (dermatitis and asthma), Alzheimer's disease, and atherosclerosis [7,8,60,63,64]. Only one study performed in humans ($n = 90$) reported that topical artesunate was effective against allergic dermatitis and photosensitive lesions (eczema, erythema multiforme, polymorphous light eruption, *hygroa aestivale*) and moderately effective against atopic dermatitis, psoriasis vulgaris, and dermatomyositis [65]. Unfortunately, we could only read the abstract as the article was not available in English and no detail was given on the study design and its methodology. Therefore we cannot draw any conclusion from this study.

3.2.3. Anti-hemorrhagic activity of artesunate and artemisinin derivatives

Subarachnoid hemorrhage (SAH) is a devastating cerebrovascular disease, responsible for a high morbidity and case fatality. In animal models, artesunate managed to preserve the blood-brain barrier integrity and improved neurological outcomes after SAH [7]. Its mechanisms of action are the activation of Claudin 3 and 5 (blood-brain barrier proteins forming tight junction), the inhibition of pro-inflammatory mediators in BV2 microglial cells, the inhibition of vascular smooth muscle cells, and the decrease in leukocyte adherence and accumulation in brain vessels (anti-ICAM1 activity, as in cerebral malaria) [7]. No study was performed in humans presenting with SAH or other cerebrovascular diseases such as intracerebral hemorrhage or ischemic cerebrovascular disease, intracranial aneurysm, or malformation, etc. Further studies are required to assess the efficacy of artesunate in these cerebrovascular diseases.

4. Conclusion

Artesunate and artemisinin derivatives are indicated as the first-line treatment of malaria. In humans, they demonstrated efficacy in the curative treatment of schistosomiasis but only in combination with praziquantel. Artesunate monotherapy may not be beneficial for patients presenting with chronic schistosomal disease. However, questions remain about the efficacy of artesunate during the invasive stage of the disease because its activity affects the early stages of the *Schistosoma* spp. parasite and artesunate could be efficient. Additional clinical trials are required to elucidate the effect of these combinations in various situations. Findings seem promising in the treatment of multidrug-resistant CMV with mild infections but data is scarce and still controversial. Artesunate and artemisinin derivatives could be interesting in cervix, breast, colorectal, and lung cancers, but the studies do not enable to draw any conclusion on their efficacy yet. Clinical studies are needed to assess the relevance of artemisinin derivatives both as anti-inflammatory and anti-hemorrhagic drugs. Finally, more trials in humans are required to assess the efficacy of artesunate and artemisinin derivatives in other diseases than malaria. No clear recommendation can be formulated so far.

Contribution of authors

AR performed the literature analysis and wrote the article.
SJ supervised this work and reviewed the article.
FB, CR, MT, EC, and PB reviewed the article.

Disclosure of interest

Jauréguiberry *déclare avoir des liens d'intérêts avec Sigma Tau pour des interventions ponctuelles et avoir des intérêts indirects avec Guilin et Walter Reed Army Institute.*

Buffet, Roussel: *intérêts indirects avec Guilin et Walter Reed Army Institute.*

Raffetin, Bruneel, Thellier, Caumes declare that they have no competing interest.

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