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Review

Artesunate to treat severe malaria in travellers: review of efficacy and safety and practical implications

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Abstract

Background: Artesunate (AS) is the WHO first-line treatment of severe malaria in endemic countries, in adults and children. However, despite solid evidence that AS is safe and more effective than quinine in endemic areas, its deployment in non-endemic areas has been slow, due in part to the absence of a full good manufacturing practice (GMP) qualification (although prequalification has been granted in 2010). Prospective comparative trials were not conducted in travellers, but several retrospective studies and case reports are providing insights into the efficacy and safety of AS in imported severe malaria.

Methods: We performed a systematic review on AS use in non-endemic areas for the treatment of imported severe malaria, using the Prisma method for bibliographic reports. Post-AS delayed haemolysis (PADH) was defined by delayed haemolytic episodes occurring 7–30 days after treatment initiation. We summarized prescription guidelines and generated answers to frequently asked questions regarding the use of AS in travellers with severe malaria.

Results: We analysed 12 retrospectives and 1 prospective study as well as 7 case reports of AS treatment in 624 travellers. Of 574 patients with reported outcome, 23 died (4%). No death was attributed to AS toxicity. Non-haematological side effects were uncommon and mainly included mild hepatitis, neurological, renal, cutaneous and cardiac manifestations. PADH occurred in 15% of the treated patients. No death or sequelae were reported. Overall blood transfusion was administered in 50% of travellers with PADH.

Conclusion: AS is highly efficacious in travellers with severe malaria. The frequency of PADH supports the need of weekly follow-up of haematological parameters during 1 month. Full GMP qualification for the drug and rapid approval by drug agencies is warranted, backed by clear recommendations for optimal use.

Key words: Artesunate, imported malaria, travellers, post-artesunate delayed haemolysis, anaemia

Introduction

'A handful of qinghao immersed with 2 l of water, wring out the juice and drink it all'. Here is how Ge Hong (284–346 CE) first referred to medicinal herb *Artemisia annua* L. (qinghao in Chinese) for treatment of malaria symptoms in his *Handbook of Prescriptions for Emergencies*. More than 1600 years later, the Chinese project 523 led by Pr Tu Youyou, drawing on traditional Chinese medicine, has isolated from *A. annua* a non-toxic, neutral extract that induced 100% parasite clearance in animal models of malaria. In 1972, this team isolated and purified by crystallization the active component of the extract: the qinghaosu (or artemisinin) and determined the stereo-structure (a sesquiterpene lactone) in 1975. They then discovered that reducing the ketone component (forming dihydroartemisinin) led to a more stable and 10 times more effective molecule than

artemisinin, with much less frequent malaria recurrences during treatment with these derivatives.[1] In 2015, the work conducted by the project 523 was internationally recognized and its team leader Pr Tu Youyou was awarded the Nobel Prize in Physiology and Medicine 'for her discoveries concerning a novel therapy against Malaria'.

The use of artesunate (AS), a derivative from artemisinin compound, in severe malaria was introduced in endemic areas on the basis of two large randomized clinical trials that showed a 35% reduction in death rates in adults in Asia and a 22.5% reduction in children in Africa when AS was compared with quinine.[2,3] In contrast to quinine, AS action on early circulating ring-stages reduces the risk of sequestration of red blood cell (RBC) infected with mature forms of *Plasmodium falciparum* and related clinical manifestations of severe malaria.[4] The anti-malarial activity is linked to the endoperoxide moiety (artemisinin derivatives that lack this moiety are devoid of parasite-killing effect)[5] but the exact mechanisms of action are still controversial. A widespread assumption is that artemisinin derivatives are pro-drugs activated by the cleavage of the endoperoxide bridge in the presence of ferrous iron or haem (Fenton-type reaction) that generates reactive oxygen species and carbon-centred radicals directly toxic on the intra-erythrocytic parasite.[6] The rapid activity of these drugs on circulating ring stages stops their development to the trophozoite stages and therefore inhibits in a few hours the sequestration process (rosetting and cytoadherence).[4,7] In contrast with other anti-malarial drugs (quinine, mefloquine, pyrimethamin), artemisinin derivatives act on almost all intra-erythrocytic parasite stages, including early rings, in addition to late trophozoites and schizonts (responsible for cytoadherence), and have also an action on immature sexual forms (but not on stage V gametocytes responsible for transmission) but have no killing activity on hepatic stages. Artemisinins induce a rapid and early clearance with up to a 10 000-fold reduction in parasite biomass per asexual cycle.[7]

In 2010, WHO has introduced the clear recommendations of using intravenous (IV) AS in all patients with severe malaria—adults, children and pregnant women—including those infected with non-*falciparum* species.[8,9] Despite solid evidence that AS is superior to quinine, its deployment in non-endemic areas has been slowed by the lack of a full WHO good manufacturing practice (GMP) qualification, although prequalification has been granted in 2010 (Guilin Pharmaceutical Company, Guilin, China), and the absence of prospective clinical safety trials including travellers. Several studies have supported the use of AS in severe imported malaria, despite the description of a new adverse event in travellers, consisting in delayed haemolytic episodes termed post-AS delayed haemolysis (PADH). We conducted here a systematic review to assess the efficacy and the safety of AS in travellers with a focus on the occurrence of haematological adverse events.

Methods

We performed a systematic analysis on the use of AS in non-malaria endemic areas for the treatment of imported severe malaria. Clinical reports, in English or French where selected according to PRISMA guidelines.[10] The literature search was made in Pubmed/Medline and Web of science in July 2016 using the following keywords: 'AS' and 'travellers' or 'imported

malaria' or 'anaemia' or 'haemolysis'. Reports were then selected according to relevance of title and abstract, and finally full-text articles were assessed for eligibility.

Case definition for PADH was a delayed haemolytic episode occurring 7–30 days after treatment initiation. Based on this analysis and on published recommendations, we summarized prescription guidelines and generated answers to frequently asked questions (FAQ) regarding the use of AS in travellers with severe malaria.

Results

We identified 20 relevant articles reporting a total of 624 travellers treated with AS for imported malaria.[11–30] Table 1 presents the results and details of a systematic review on the use of AS in travellers. Data available in the literature were mostly case-reports (7)[16,18,22–24,28,29] and retrospectives studies (12),[11–15,17,19–21,26,27,30] except for one prospective study.[25]

Efficacy of AS in Imported Severe Malaria

In 2008 in Norway, Mørch *et al.* published the first description of the use of IV AS in Europe in nine travellers with severe falciparum malaria. All patients survived with no sequelae and no adverse events were reported.[12] Through the published studies, on the 574 cases where outcome was reported, 23 patients died (4%) but no death attributed to the treatment was reported. Treatment regimen differed depending on the study but consisted essentially in IV AS (except for the use of rectal route in one study),[21] in first or second line (mostly after IV Quinine) alone or in association with several anti-malarial drugs. In a vast majority of cases, patients were treated for severe malaria (expect for 13 patients in one study who were treated for uncomplicated malaria).[20]

Safety of AS in Imported Severe Malaria

Studies conducted in travellers reported a good overall tolerance despite a high proportion of delayed haemolytic episodes (PADH). Data on other adverse events were reported in 15 studies[12–14,16–22,24,25,27,29,30] (in only a subset of patients in two studies),[21,27] information was thus available for 465 patients. In total, 27.7% of patients (129/465) declared at least one adverse event during treatment or after receiving AS but most of those were retrospectively attributed to malaria or to a concomitant treatment (mainly quinine). Of note, one study reported adverse events in 92.2% (94/102) of patients, including anaemia (65% of patients) and increased hepatic enzyme level (49%), most of them being considered malaria-related whereas no grade four events were considered 'definitively' related to AS.[30] Finally, 28 (6%) adverse events were considered as possibly related to AS: 5 neurological syndromes (1%), 3 temporary deteriorations in renal function (0.6%), 3 cutaneous (0.6%) and 3 cardiac (0.6%) manifestations (including QTc lengthening episode and transient bradycardia in 1 and 2 patients, respectively),[25] 1 severe arterial ischaemia (0.2%), 1 episode of hypertension (0.2%), 8 cases of elevation of liver enzymes (1.7%) and 1 of hyperkaliaemia (0.2%), 2 'minor adverse events' not specified (0.4%) and 1 case of early haemolysis (0.2%). Three studies have reported the use of AS during pregnancy (7 cases)[12,25,30] without reported fetal or maternal toxicity for six of them and one case of

Table 1. Systematic review of imported malaria treated with AS

Reference	Year(s)	Country	Number of AS-treated patients	Clinical presentation	Follow-up duration	Study design	Treatment detail	Outcome	Haemolytic anaemia (PADH lato sensu)	PADH-related transfusion	Other AEs	PADH case definition
Tang et al.[11]	1991–2002	Taiwan	2	Severe falciparum malaria (cerebral)	N/A	Retrospective	AS IV + Q + Doxy ± PQ	Recovery 2/2 (100%)	N/A	na	N/A	na
Morch et al.[12]	2006–08	Norway	9	Severe falciparum malaria	4 weeks	Retrospective	IV AS + Doxy (7/9) IV AS (1/9) IV AS + Clinda (1/9)	Recovery 9/9 (100%) no sequelae, no recrudescence	0/9 (0%)	na	No (1 pregnant women—3rd trimester—delivered a healthy child at term)	na
Kano[13]	2001–07	Japan	5	Severe or drug resistant falciparum malaria	N/A	Retrospective	IV AS + MQ	Recovery 5/5 (100%)	2/5 (40%)	2/2 (100%)	Post-malaria neurological syndrome (1/5)	na
Bartoloni et al.[14]	2008–09	Italy	8 (5 children)	Severe falciparum malaria	2–25 days in hospital, follow-up duration N/A	Retrospective	IV AS + IV Q	Recovery with no sequelae 7/8 (87.5%) Mortality rate 1/8 (12.5%) Recrudescence 5 days after the end of treatment 1/8 (12.5%)	0/8 (0%)	na	Cinchonism (2/8) hypoglycaemia (2/8) attributed to quinine	na
Mali et al.[15], (MMWR) Morbidity and Mortality weekly report	2010	USA	39	Severe falciparum malaria	N/A	Retrospective	IV AS 1st line or 2nd line after IV Q	Mortality rate 5/39 (12.8%)	N/A	na	N/A	na
Callender and Hsue[16]	2009	Hawai'i	1	Severe falciparum malaria	6 months	Case report	IV AS	Recovery 1/1 (100%)	0/1 (0%)	na	No	na
Zoller[17]	2006–10	Europe	25 (1 child)	Severe falciparum malaria	N/A	Retrospective	IV AS 1st line (22/25) IV AS 2nd line (3/25)	Recovery 25/25 (100%)	6/25 (24%) 3 persistent 3 PADH stricto sensu	5/6 (83%)	No	N/A
Caramello et al.[18]	2011	Italy	1	Severe falciparum malaria	40 days	Case report	IV AS 2nd line	Recovery 1/1 (100%)	1/1 (100%)	1/1 (100%)	No	N/A
Eder et al.[19]	2009–11	UK	24	Severe falciparum malaria	N/A	Retrospective comparative study IV AS vs IV Q	IV AS 1st line (16/24) IV AS after 1 dose of IV Q (8/24)	Recovery 24/24 (100%)	1/24 (4%) delayed haemolysis Day 15 with Coombs +	1/1 (100%)	No	N/A
Kreeftmeijer-Vegter et al.[20]	2007–10	Netherlands, Belgium	68	Severe falciparum malaria (55/68) non-severe malaria (13) (1/68 = P. vivax, 1/68 = P. ovale)	N/A	Retrospective	IV AS 1st line monoherapy or in association (43/68) IV AS in 2nd (25/68)	Mortality rate in severe malaria 2/55 (3.6%)	7/55 (13%)	4/7 (57%)	1 Neurological syndrome concomitant to haemolysis at D30. No other AEs reported to AS	N/A
Rolling et al.[21]	2006–12	Germany	8	Severe falciparum malaria	4 weeks	Retrospective comparative study IV AS/IV Q	IV AS (4/8) or Rectal AS + IV Q (4/8) vs IV Q	Recovery 8/8 100%	5/8 (63%) delayed haemolysis	3/5 (60%)	temporary deterioration in renal function (3/5)	Any decrease in median Hb and any increase in median LDH between Weeks 2 and 3
Paczkowski et al.[22], (MMWR)	2008–13	USA	2	Severe falciparum malaria	13 and 26 days	Case report	IV AS	Recovery 2/2 (100%)	2/2 (100%)	2/2 (100%)	No	N/A
Boillat et al.[23]	2012–15	Switzerland	4	Severe falciparum malaria	At least 4 weeks	Case report	IV AS	Recovery 4/4 (100%)	4/4 (100%) (uncertain diagnostic for 1 case with multifactorial anaemia)	3/4 (75%)	N/A	Hb drop + haemolysis (low haptoglobin, increased LDH) after Day 7 or continuing haemolysis starting from and around Day 7 and persisting beyond Day 14
Lee et al.[24]	2012	Canada	1	Severe falciparum malaria	6 weeks	Case report	IV AS	Recovery 1/1 (100%)	1/1 (100%)	1/1 (100%)	No	Decrease in Hb combined with an increase in LDH between Weeks 2 and 3
Jauréguiberry et al.[25]	2011–13	France	123	Severe falciparum malaria	>8 days for 78/123	Prospective	IV AS	Mortality rate 6/123 (4.8%)	21/78 (27%)	1/21 (<5%)	Cutaneous 3/123 (2.4%) Neurological 4/123 (3.2%) Cardiac 4/123 (3.2%) Hypertension 1/123 (0.8%) Elevated level of ALT 8/123 (6.5%) Hyperkaliaemia 1/123 (0.8%)	>10% decrease in Hb level + >10% increase in LDH level after Day 8
Kurth et al.[26]	2006–14	Europe	70	Severe falciparum malaria		Retrospective comparative study IV AS/IV Q	IV AS 1st line (60/70) IV AS 2nd line (3/70) IV AS + IV Q (7/70)	Mortality rate 1/70 (1.4%)	19/70 (27%)	N/A	N/A	N/A

(continued)

Table 1 Continued

Reference	Year(s)	Country	Number of AS-treated patients	Clinical presentation	Follow-up duration	Study design	Treatment detail	Outcome	Haemolytic anaemia (PADH lato sensu)	PADH-related transfusion	Other AEs	PADH case definition
McCarthy et al.[27]	2001–13	Canada	129	Severe falciparum malaria	N/A	Retrospective comparative study IV AS/IV Q	IV AS	Mortality rate 1/92 (1%)	2/89 (2.2%)	at least 1 (data N/A for the second case)	minor 2/89 (2.2%), Serious 1/89 (1.1%) (early haemolysis) Other 2/89 (2.2%) (determined retrospectively as unrelated to the treatment)	N/A (one case of 'delayed haemolysis' occured at Day 6)
Chavada et al.[28]	N/A	Australia	1	Severe falciparum malaria	N/A	Case report	IV AS	Recovery 1/1 (100%)	1/1 (100%)	1/1 (100%)	N/A	Decline in Hb level ≥ 10%, haptoglobin level ≤ 0.1g/l and LDH level > 390 U/l at least 7 days after initiation of IV AS
Charles et al.[29]	2013–14	Canada	2	Severe falciparum malaria	3.5 months (1/2), 20 days (1/2)	Case report	IV AS	Recovery 2/2 (100%)	2/2 (100%)	2/2 (100%)	No	Decline in Hb level ≥ 10%, haptoglobin level ≤ 0.1g/l and LDH level > 390 U/l at least 7 days after initiation of IV AS
Twomey et al.[30]	2007–10	USA	102	Severe malaria	7 days	Retrospective	IV AS alone (56/102) or in association (46/102)	Mortality rate 7/102 (6.9%)	0/102 (0%)	na	92.2% of patients (most of them attributed to the disease). No grade 4 AEs was considered 'definitively' related to AS 2 pregnant women delivered healthy infants	na
Total 20 (13 studies, 7 case reports)			624			Retrospective (12/20), prospective (1/20), case reports (7/20)		Mortality rate 23/574 (4%)	74/485 (15.3%)	27/54 (50%)	129/465 (27.7%) 28/465 (6%) attributed to AS or not specified	

IV AS, intravenous artesunate; IV Q, intravenous quinine; Doxy, doxycycline; Clinda, clindamycine; PQ, primaquine; MQ, mefloquine; N/A, not available; na, not applicable; PADH, post-AS delayed haemolysis; AEs, adverse events; Hb, haemoglobin; LDH, lactate dehydrogenase; ALT, alanine aminotransferase.

miscarriage.[25] Follow-up duration varied from 7 days[30] to 6 months[16] whereas it was not mentioned in 10 studies.

The most frequent reported adverse event was PADH. This complication seems AS-related as it was not described in quinine-treated patients[21] and as search for conventional causes for haemolysis was usually negative when performed.[13,18,20,31,32] The very first case was probably described in 2002 in Japan.[13,33] The patient had haemolysis and jaundice at Day 11 and survived without sequelae but needed RBC concentrates transfusion. No other cases were reported until 2011 when the use of AS for severe malaria started to spread in non-endemic countries. Zoller *et al.*[17] described the first case series (6 cases) of late or persistent haemolysis following treatment. Definition of PADH is, however, not univocal through published studies. Most of them did not use a precise case definition. The first[34] and currently accepted[35] objective definition of PADH associates a decrease in haemoglobin (Hb) level > 10% associated with an increase in lactate dehydrogenase (LDH) level > 10% after Day 8 post-treatment initiation. Others,[36] used a broader definition including any decrease in median Hb and any increase in median LDH between the second and the third week after treatment associated with low haptoglobin at the end of the second week. The incidence of delayed haemolysis varies widely depending on the studies (and case definition) from 0%[12,14,16,30] to 63%.[21] In our systematic analysis PADH occurred in 15.3% (74/485) of patients with available follow-up data, 50% (27/54 patients with available transfusion data) requiring transfusion. In the only prospective study to date in travellers, PADH occurred in 27% of patients followed after D8 (21/78) but only 15% of those cases had haemoglobin levels < 7 g/dl and < 5% (1 patient) required transfusion.[25] No death or sequelae have been attributed to the occurrence of PADH so far. No specific treatment for PADH was published. Corticosteroids were two times used[19,20] but with unclear influence on the natural course of the haemolytic episode.

Factsheets and Frequently Asked Questions

AS is a new therapeutic for most clinicians in non-endemic countries for malaria. Table 2 summarizes answers to FAQ and information published about the use of AS in severe malaria[9,37] and practical implications.

Discussion

This review reports the high efficacy and reasonable safety of AS in the treatment of severe malaria in non-endemic areas.

No comparative randomized and controlled trials have been conducted in travellers for ethical reasons,[38] but studies reviewed here, reporting the use of AS in travellers in several countries, confirmed that the drug is well tolerated and efficient. Clinical impact of AS on mortality is, however, difficult to assess in high level of care countries, as mortality of severe malaria is already very low in quinine-treated patients (5.2% in a recently published prospective trial).[39] In our review, 4% of patients with reported outcome died, which is close to 5% mortality rate reported in the only prospective study conducted in travellers.[25] Four non-randomized studies have compared retrospectively quinine with AS in travellers[19,21,26,27] but the

number of AS-treated patients with reported outcome was not sufficient to conclude on the improvement of mortality while the design of these studies were not appropriate.

The efficacy of artemisinins seems to be principally due to the peak concentration (Cmax) while the drug exposure level (Area under the curve AUC) and drug exposure time (half-life) would be of minor significance. Furthermore, the parasite-killing activity is dose-dependent.[40] In travellers treated with AS, parasite clearance is mainly due to pitting.[41] Pitting is an original process whereby the parasite, which has been killed by the drug, is removed from its host RBC without haemolysis when passing through the inter-endothelial slits of the spleen. The dead parasite is thus retained in the spleen and eliminated by resident phagocytic cells while the 'once-infected' RBC returns to general circulation.[42] Thus, AS treatment leads to a rapid decrease in parasitaemia and the inhibition of cytoadherence[4] without destruction (at least initially) of hosts RBC.[42] In splenectomized patients treated with AS, because of the absence of pitting, complete clearance of RBC containing dead parasite remnants is much longer (days or even weeks) than in patients with a spleen.[43] These observations on splenectomized patients confirm that pitting is a spleen-specific process. Pitting can be observed without treatment but usually at a low rate (<5%). In quinine-treated patients, the pitting rate generally does not exceed 20–25%. However, in African immune populations, while pitting contributes substantially to parasite clearance, passively and naturally acquired immune mechanisms operating faster than pitting do exist.[41]

Several hypotheses have been proposed to explain the pathogenesis of PADH, including late toxicity due to manufacturing problems, suppressive effect on the bone marrow, auto-immune haemolysis or host factors (enzymes deficiencies, haemoglobinopathies or differences in pharmacokinetics). None of these have been solidly substantiated by data so far.[44] Recent observations in a cohort of patients with severe imported malaria strongly suggest that PADH is related to pitting. Typical delayed haemolytic episodes were indeed linked to the delayed clearance of once-infected RBC that were initially spared by pitting during AS treatment.[34] PADH can thus be predicted by the determination of the peak concentration of once-infected RBC (between Days 2 and 8). The threshold 0.18 g/l predicts PADH with 89% sensitivity and 83% specificity.[34] This quantification is currently performed by flow cytometry at reference centres. Development of a simpler test is now needed to allow the prediction of PADH in endemic areas. The occurrence of PADH is not an immuno-allergic reaction and should not contraindicate the use of AS in case of a subsequent access.

PADH is a matter of concern for management of patients but does not undermine the survival benefit provided by this new class of compound, if accurate prediction and management are implemented, including weekly follow-up during 4 weeks post-treatment.[37] Thus, close supervision of haematological parameters is absolutely necessary following the treatment as long as no predictive marker for PADH is available (Table 2). In October 2013, WHO published an information note which stated that 'the therapeutic benefits far outweigh the risk of artemisinin-related adverse events, including post-treatment delayed haemolytic anaemia'.[45]

Table 2. FAQ and factsheets about IV AS for imported severe malaria

FAQ? and factsheets	Answers
How to prescribe AS?	WHO recommends IV or IM AS to be administrated at 2.4 mg/kg/dose for at least 24 h and as long as oral route is not possible for all patients with severe malaria (at list one criterion).[9]
	In children under 20 kg, WHO recommends to increase the dose of parenteral AS to 3 mg/kg/dose to ensure equivalent drug exposure.[9]
Which formulations of AS?	Available AS formulation in Europe is a powder of 60 mg to be reconstituted (with bicarbonate de sodium 1ml) and diluted (saline serum 5ml) to reach 10 mg/ml final concentration.
	Concentration of the final reconstitution solution must be 10 mg/ml for IV solution or 20 mg/ml for the IM use.
	Blood DHA peak is reached more rapidly with IV than IM route.
Which regimen?	Conventional regimen consists on an injection at 0, 12 and 24 h after admission and then every 24 h until 7 days.
How many doses?	Duration of injection should be maintained below 3–4 ml/min on each infusion.
	Parenteral administration will be continued until treatment can be administered orally or if severe criteria persist (i.e. consciousness impairment, renal failure).
How to switch?	A switch to oral therapy by an ACT (artemether-lumefantrine or DHA-piperaquine) for 3 days is mandatory after completion of at least 24 h of AS IV (3 doses) to prevent recrudescence of parasitaemia and symptoms, a risk related in part to the short half-life of AS.
	A time interval (8–12 h) seems to be necessary between the end of AS and the first dose of oral ACT.
How to manage AS with multiorgan failure during severe malaria?	No dosing adjustment is necessary for patient with renal or hepatic function impairment as the half-life is very short.
	However, no data are available to date on pharmacokinetics and dynamics in those patients (especially patients requiring dialysis) and other specific categories (obesity, elderly).
What about pregnant women?	AS could be used for pregnant women in all trimesters.[9]
	A recent review of the literature suggests lower-maximum concentrations and exposure of DHA, after oral administration of artemether, AS and DHA in pregnant women[59] with uncomplicated malaria but very few data are available to date for IV AS in severe malaria.
	Treatment with parenteral AS in pregnant women should thus be monitored very closely for safety but also for efficacy as pharmacokinetics and dynamics could be modified by pregnancy.
How to monitor the efficacy and safety of AS during and after severe malaria attack?	Patient follow-up should be performed on Days 3, 7, 14, 21 and 28 to assess treatment efficacy and safety and should consist in physical examination and measure of haemolysis bio-markers (Haemoglobin, LDH, haptoglobin, reticulocytes) to detect the occurrence of PADH. Parasitaemia determination (thin and/or thick smear) should be performed on Days 3, 7 and 28.[37]
	Patient should be informed of the PADH and warning signs and symptoms that warrant immediate referral to the hospital.
How to manage overdose of AS?	There are few data about overdosing of AS.
	A case of overdose has been documented by Guilin (http://guilinpharma.com/en/en/new_drug/Artesun_Clinical_Data.html) in a 5-year-old child who was inadvertently administered rectal AS at a dose of 88 mg/kg/day over 4 days. The overdose was associated with pancytopenia, melena, seizures, multiorgan failure and death.
	There is no specific treatment for overdose but blood count and EKG should be closely monitored and treatment consists in general supportive measures.

IV, intravenous; IM, intramuscular; ACT, artemisinin-based combination therapies; DHA, dihydroartemisinin, active compound of artemisinine; AS, artesunate; PADH, post-AS delayed haemolysis; LDH, lactate dehydrogenase; EKG, electrocardiography.

The incidence of PADH in this review was 15%. This proportion can be overestimated as the most severe cases are more likely to be reported. On another hand it can also be underestimated by a short follow-up.[30,31] Of note the incidence reached 27% in the prospective study conducted in travellers.[25]

The haemolysis generally corrects spontaneously in a few days to few weeks (usually <6, personal data) and the only treatment that can be required is transfusion according to haemoglobin level and patient tolerance to anaemia. Although decrease in haemoglobin level is generally mild, cases of severe anaemia with severe complications have been reported including a case of renal impairment by haemoglobinuria in endemic area.[46] These episodes were not previously described in large clinical trials conducted in endemic areas.[2,3] Since then, Rolling *et al.* conducted a prospective study in 72 African children treated with IV AS and found an incidence of PADH of 7%.[47] Patients with PADH were younger and had higher-initial parasitaemia. A second study enrolling children and adults in Democratic Republic of the Congo found delayed haemolysis in 11.4% of cases, all clinically manageable and rapidly resolving.[48] Simple biological parameters such as high parasitaemia and high level of haemoglobin at Day 0 could be major risk factors but there are not sufficient to provide risk assessment for PADH.[22,24,27,29] The responsibility of the Chinese product has been debated as no cases of PADH were described in north America until recently but since 2014 several cases have been reported both in USA and Canada.[22,24,27,29] Late haemolysis depends of generated once-infected RBC, the time onset of treatment regarding parasitaemia and stage of development of the parasite.

Since PADH has been shown to be linked to the pitting process, all artemisin derivatives can theoretically be responsible for the occurrence of a delayed haemolysis. Cases have been reported in patient treated with artemisinin-based combination therapies (ACT) but the intensity of haemolysis was mild.[49–52] ACT are mostly used for the treatment of uncomplicated malaria with generally low initial parasitaemia which makes the risk of a severe PADH low. In our opinion, the risk for PADH after ACT should be considered in case of treatment for a patient with high parasitaemia without any other signs for severe malaria.

Except from the recently described PADH, non-haematological adverse events (hepatic, neurological or cardiac) were previously described or published by the manufacturer (Summary of product characteristics Guilin). In a meta-analysis on artemisinin derivatives including 108 trials (9241 patients), no drug-related serious adverse event or severe significant toxicity were reported.[53] One of the most frequent adverse event reported in travellers is liver toxicity. It is well known but it is infrequent (0.9–4.5%), mild and regresses in all cases without sequelae.[53,54] It reaches almost 2% in our review. However, most of these reported elevated liver enzyme cases can also be malaria-related. AS showed a good cardiac tolerance in current practice[55,56] but can cause bradycardia when used at high dose (15 mg/kg).[57] Here, we found three cases of cardiac toxicity.[25]

In Europe, AS is not licenced but was recently granted an orphan drug compassionate use status (European Medicines Agency EMA). To our knowledge, there is no available AS manufactured under GMP in Europe. In the USA, a GMP formulation developed by the Walter Reed Army Institute of Research is available since 2004. Since 2011 with the help of Medicine for Malaria Venture to improve the manufacturing process the Chinese product is prequalified by the WHO.[58] This is not, however, a full GMP certification and AS does not have marketing approval in the ICH (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use) zone. In France, Belgium and Netherlands the product is available through a named patient program.[20,25] Considering the emergency context for use of AS to treat severe malaria, AS should be stocked ahead of time in local hospitals and infectious diseases units for immediate availability upon request by clinicians. Any centre regularly treating malaria patients should stock AS and follow local policy to get the product. If AS is not available, IV quinine should be used instead as any delay in the treatment of severe malaria can increase the risk of mortality. Lack of GMP manufactured AS is one major disincentive to the use of this new class treatment for all imported severe malaria. It is now time to get and deploy a full GMP qualified AS, as the medical benefit of this new treatment is priceless.

Conflict of Interest

C.R, A.N and S.J. collaborate with Guilin Laboratories; P.B. provided expertise and collaborates with Fast-Track Drugs & Biologics LLC and Sigma-Tau Pharmaceuticals, is engaged in a collaboration with Guilin Laboratories and has provided expertise to Sanofi Aventis Research & Development. The remaining authors declare no competing financial interests.

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