Artemisinin Derivatives

History

- Active extract of *Artemisia annua* (Qinghao, or sweet wormwood), used for centuries in traditional Chinese herbal medicine. Discovered by Chinese scientists during the Cultural Revolution and first published in Western medical literature in 1979. Tu Youyou shared in the 2015 Nobel Prize in Medicine for her role in its discovery.
- Artemisinin has been superseded by four main derivatives: artesunate, artemether, dihydroarteminisin, and artemotil. Fully synthetic trioxolanes have been developed: arterolane is now available in India in fixed dose combinations with piperquine. Another (artefenomel) has progressed through phase II trials and has potential to be used as a single-dose therapy.

Chemistry and Structure

- Consists of a peroxide bridge within a 1, 2, 4 trioxane configuration, containing a sesquiterpene lactone ring with an endoperoxide bridge essential for antimalarial activity. Artemether and artemotil are lipophilic methyl ethers. Artesunate (hemisuccinate) is water soluble and the only agent available as an intravenous formulation (as well as oral, IM and PR formulations). Artemether is available orally or as IMI suspended in peanut oil.

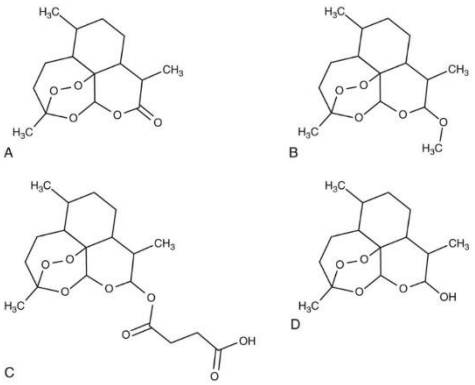


FIGURE 40-2 Structures of artemisinin derivatives. **A,** Artemisinin. **B,** Artemether. **C,** Artesunate. **D,** Dihydroartemisinin.

Spectrum

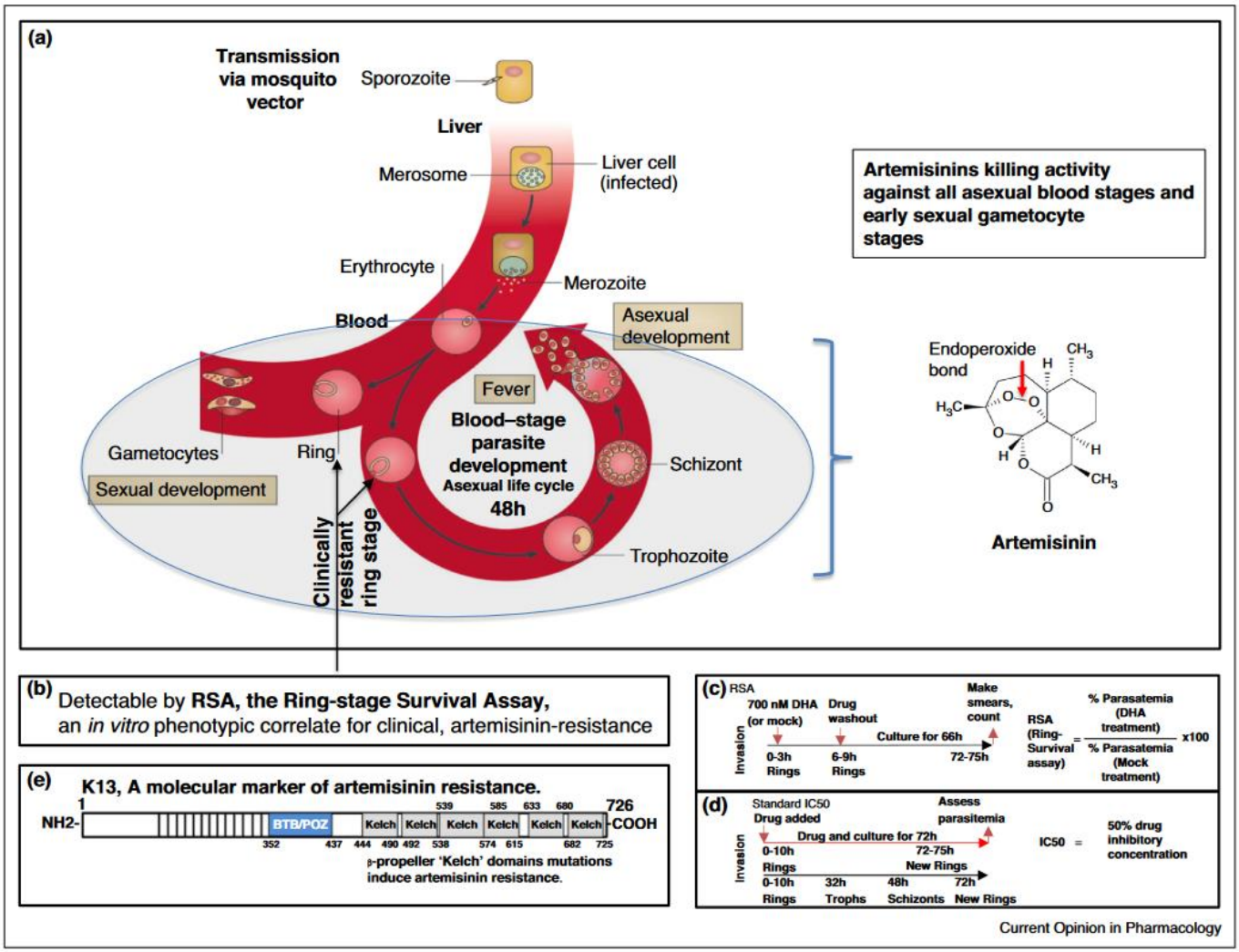
- Excellent efficacy against all human malaria parasites, including multiresistant strains of *Plasmodium falciparum* and *P. vivax.* Reduces production of gametocytes, a high carriage of which is associated with recrudescence.
- Also has *in vitro* activity against *Shistosoma, Fasciola, Opisthorchis, Clonorchis* and *Leishmania,* however susceptibility is reduced. Young developmental stages appear to be more vulnerable. However, for schistosomiasis it appears to have no increased benefit when paired with praziquantel over praziquantel alone. Artemisinin compounds inhibit *in vitro* growth of *Trypanosoma cruzi*, but not in mice models. Artesunate also has *in vitro* activity against CMV, HSV 1 and HBV. Artesunate has been used in a case report of a 12 year old HSCT recipient with forscarnet – resistant and ganciclovir resistant CMV, resulting in a 1.7 – 2.1 log reduction in viral load.

Mechanisms of Action

- Remains to be fully elucidated, but is dependent on the endoperoxide dioxygen bridge. The most widely accepted theory is that the interaction between the peroxide bridge and ferrous iron (Fe^{2+}) leads to the formation of hydroperoxide free radicals that rearrange into carbon-centred radicals and reactive metabolites. These radicals may then interact with parasite targets (causing damage to parasite organelles), haemin and red cell membranes, although the potency of these agents against malarial parasites suggests a parasite specific mechanism of action.
- Other purported mechanisms include disruption of parasite calcium homeostasis, translationally controlled tumour protein homolog (TCTP) and the mitochondrial electron transport chain.

Mechanisms of Resistance

- Initially emerged along the Cambodia/Thailand border between 2001 and 2009, and since has been reported from the western border of Thailand and other regions in the Greater Mekong Region, which is also where chloroquine, sulfadoxine-pyrimethamine and mefloquine resistance was first documented. The overall efficacy of both artesunate-mefloquine and DHA-piperaquine combinations is severely reduced in this region.
- Resistance is indicated by a delayed parasite clearance rate. Modelling of clearance rates indicates that resistant phenotypes are associated with decreased inhibition of the immature ring stages and is associated with polymorphisms in *pfkelch13 (*K13), which is predicted to be a substrate adapter of an E3 ligase. This may have a role in cellular homeostasis and controlling proteolysis via phosphatidylinositol-3-phosphate (PI3P). Orthologues of *kelch* in cancer confers resistance to drugs that induce "proteopathy" in tumours.
- Resistance can be demonstrates *in vitro* via the Ring Survival Assay, which exposes ring-stage parasites to dihydroartemisin (DHA) for 6 hours, and then allow normal development after washout and assessment of new ring forms at 72 hours.



PK/PD

- Artemisinins are absorbed rapidly after oral administration – maximum plasma concentration occurring in less than 1 hour for artesunate and 1-3 hours for artemether. IM absorption of artemether is highly variable.
- Artesunate and artemether are rapidly converted to dihydroartemisinin (DHA) after extensive first pass metabolism. Maximum concentrations of DHA occur at 10 minutes after IV injection of artesunate, 30 minutes after IM injection and 1-2 hours after oral administration.
- The bioavailability of DHA is doubled in patients with malaria compared with healthy volunteers and in the acute phase of infection compared to convalescence, but has a fourfold reduction in pregnant women.
- Metabolism of artemisinin involves CYP2B6, however artemether and arteether are metabolised to DHA by CYP3A4. DHA itself is metabolised by cytochrome P 450, with elimination in bile as inert glucuronides. The elimination half-life of DHA after artesunate is < 1 hour, with artemether being significantly longer (2-12 hours). Because of this rapid elimination, a prolonged course /partnering with another drug with a longer half-life is necessary for cure and to protect against emergence of resistance. The dosing of artesunate or artemether/lumefantrine does not need to be modified for hepatic or renal failure (no data in severe impairment).

Clinical Use

- Artemisinin based combination therapy (ACT) has been crucial in reducing global malaria burden: an estimated 2.74 billion treatment courses were procured by countries over the period 2010 – 2017. They are the fastest acting antimalarial class, with fever clearance typically being achieved in 20 hours and parasites in 48 hours.

- *Severe malaria*[1]*:* artesunate 2.4mg/kg IV at 0, 12 and 24hours, then once daily until tolerating orals. If travelling from the Greater Mekong Subregion: combine with IV quinine. A Cochrane metanalysis found a reduced mortality in children for artesunate compared to quinine (RR 0.76 [0.65 – 0.9]) and adults (RR 0.61 [0.5 – 0.75]).
- *Uncomplicated malaria:* artemether + lumefantrine, 4 tablets orally (adults), at 0, 8 24, 36, 48 and 60 hours, taken with fats (increases concentrations of lumefantrine up to 16x). WHO guidelines recommend 5 ACTs for uncomplicated *P. falciparum* malaria: artemether + lumefantrine, artesunae + amodiaquine, artesunate + mefloquine, artesunate + sulfadoxine-pyrimethamine and dihydroartemisinin + piperaquine.

Adverse effects:

- Artemisinin drugs have an excellent toxicity profile, with no difference in the incidence of adverse effects between derivatives. Most commonly reported reactions are nausea, vomiting and diarrhoea (all frequent symptoms of malaria). Cases of anaphylaxis and urticarial have been reported
- *Neurotoxicity:* controversial. The lipophilic compounds (artemether/arteether) have been associated with neurologic toxicity in dogs, rodents and monkeys at doses of > 15mg/kg/day for prolonged periods (> 15 days), with a toxicity predilection for the brainstem (particularly the reticular formation and vestibular nuclei). Some case reports of neurologic abnormalities following artesunate have been ascribed to artemisinin derivative toxicity, however this is not borne out in large trials. *Cardiotoxicity:* minor QT prolongation, rarely transient 1^{o} HB. Mild, transient neutropenia may occur in high doses. *Delayed anaemia:* described following artesunate, occurs 8 – 32 days following completion of therapy and may necessitate transfusion.
- *Pregnancy:* Artemether/lumefantrine is category D, with TG19 recommending avoiding this combination in the first trimester (use atovaquone + proguanil instead, WHO recommends quinine + clindamycin).

Lumefantrine:

- Aryl-amino alcohol, only available as a coformulation with artemether.
- Has complementary activity with artemether but longer acting, allowing sustained antimalarial activity to kill the residual blood stage parasites. Mechanism of action is thought to be via interaction with haeme in the parasitic food vacuole.
- Schizonticidal against the erythrocytic stages but has no activity against gametocytes, hypnozoites or the pre-erythrocytic stages.
- Slowly and erratically absorbed following ingestion – peak plasma levels within 4 – 10 hours. 90% protein bound, metabolised by the liver to desbutyl-lumefantrine (CYP3A4) (terminal half life 3-6 days, reduced to ~ 2 days in pregnant women). Coadministration of antiarrythmics, macrolides, quinolones and other CYP3A4 inducers should be avoided.

Cost – thanks Kristi!

Artesunate 60mg vial = $40 per vial (mythical 70kg person would cost $240 on the first day, then $120 per day)
Artemether 120mg/lumefantrine 20mg (Riamet) = $3.20 per tablet ($76.80 for a standard adult regimen)

References:

- John E. Bennett, Raphael Dolin, Martin J. Blaser. (2015). Mandell, Douglas, and Bennett's principles and practice of infectious diseases. Philadelphia, PA :Elsevier/Saunders,
- Grayson, M. Lindsay. (2010). Kucers' the use of antibiotics : a clinical review of antibacterial, antifungal, antiparasitic and antiviral drugs. London : Hodder Arnold
- Therapeutic Guidelines 2019
- Suresh, N. and K. Haldar (2018). "Mechanisms of artemisinin resistance in Plasmodium falciparum malaria." Curr Opin Pharmacol 42: 46-54.
- Sinclair, D., et al. (2012). "Artesunate versus quinine for treating severe malaria." Cochrane Database of Systematic Reviews(6).
- Guidelines for the treatment of malaria – Third Edition (2015) – World Health Organisation

[1] *Severe malaria* = any of: parasitaemia > 2%, ↓GCS, ↓ glucose, ↓ urine output, jaundice, respiratory distress, vomiting, severe anaemia, metabolic acidosis, AKI (TG19)