Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

Artesunate

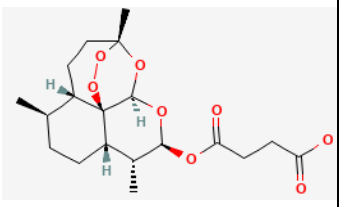
Evidence Summary

Artesunate shows evidence of anti-microbial, anti-cancer, anti-inflammatory, and anti-fibrotic effects in preclinical models. Aside from malaria, benefits in clinical trials have been modest, but well-tolerated.

Neuroprotective Benefit: Preclinical studies suggest artesunate protects against neural injury within a low dose range, but high doses could be neurotoxic. Cognitive benefits have not yet been seen in small trials for indications other than malaria.

Aging and related health concerns: Artesunate may offer some protection against a variety of pathogen-related diseases, including some forms of cancer. It also shows anti-inflammatory and anti-fibrotic effects in a wide range of preclinical models.

Safety: Artesunate has been safe and well-tolerated for the majority of malaria patients and those in clinical trials. Common side effects include gastrointestinal effects, dizziness, and fever. Rare serious effects include liver injury, kidney injury, and hemolytic anemia.

Availability: Rx	**Dose**: For severe malaria the dose is 2.4 mg/kg i.v. at 0, 12, and 24 hours, then once per day. For uncomplicated malaria (in those >36 kg) the oral dose is 200 mg/day (+ amodiaquine) for 3 days	**Chemical formula:** $C_{19}H_{28}O_8$ **MW**: 384.4 g/mol  Source: PubChem
Half-life: range 0.5-1.5 hours	**BBB**: Penetrant	
Clinical trials: Aside from malaria and other pathogen-related diseases, artesunate has been tested in pilot clinical trials for lung cancer (n=120), colorectal cancer (n=23), breast cancer (n=23), cervical cancer (n=29), and traumatic hemorrhage (n=83).	**Observational studies**: Children with cerebral malaria treated with artesunate were found to have superior long-term neurological outcomes relative to those treated with other antimalarial agents.	

What is it?

Artesunate is a water-soluble semi-synthetic derivative of artemisinin developed by Liu Xu in 1977 as an antimalarial agent [2]. Artemisinin is derived from sweet wormwood (*Artemisia annua*), and its antimalarial properties were rediscovered in 1972 by the Chinese chemist Tu Youyou, who subsequently won the Nobel Prize for this work in 2015. Artesunate has superior drug-like properties relative to artemisinin, including better oral bioavailability and blood brain barrier (BBB) penetrance. Artemisinin and its derivatives, including artesunate, are metabolized in the body to the active metabolite dihydroartemisinin, which has a slightly longer half-life. Artesunate is currently the recommended first line treatment for malaria by the World Health Organization (Malaria guidelines), and was approved by the FDA for use in severe malaria in 2020 (Press release). Based on the broad-spectrum anti-pathogen, anti-cancer, anti-inflammatory, and anti-fibrotic properties seen in preclinical studies, artesunate has begun to be tested in a variety of other indications, particularly cancer [3].

Neuroprotective Benefit: Preclinical studies suggest artesunate protects against neural injury within a low dose range, but high doses could be neurotoxic. Cognitive benefits have not yet been seen in small trials for indications other than malaria.

Types of evidence:

- 1 clinical trial testing artemether in patients with schizophrenia
- 1 clinical trial testing artesunate in patients with traumatic hemorrhage
- 1 clinical trial testing artesunate in Lyme disease
- 1 observational study following children with cerebral malaria treated with artesunate
- Numerous laboratory studies

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function:

It has not been established whether artesunate can prevent dementia. There is evidence to suggest that artesunate and other artemisinin derivatives can mitigate adverse neurological outcomes in patients with cerebral malaria. A prospective observational study including 502 Ugandan children with severe malaria in which 346 children received quinine and 156 received parenteral artemisinin therapy (artemether or artesunate) found that children receiving artemisinin derivatives exhibited less neurological deficits (adjusted Odds Ratio [OR]: 0.28, 95% Confidence Interval [CI] 0.13 to 0.59) (23.7% artemisinin derivatives vs. 41.7% quinine, p=0.007) [4]. These children also showed better behavior and executive function over a two-year follow-up period. Additionally, children treated specifically with artesunate had lower plasma levels of the inflammatory marker C-reactive protein (CRP) (beta: −1.90, 95% CI −2.56 to −1.25). A clinical trial testing a separate artemisinin derivative, artemether (80 mg/day), in patients with first-episode, untreated schizophrenia, who were *Toxoplasma gondii* seropositive, did not find evidence to indicate that artemisinin derivatives can mitigate cognitive deficits related to schizophrenia [5]. Artesunate (20 mg, four times/day) was not associated with a reduction in short term memory difficulties in patients with Lyme disease, in an uncontrolled clinical study [6].

Human research to suggest benefits to patients with dementia:

Artesunate has not been tested in dementia patients.

Mechanisms of action for neuroprotection identified from laboratory and clinical research:

Alzheimer's disease: POTENTIAL (LOW) DOSE-DEPENDENT BENEFIT (Preclinical)
Artesunate has shown protective effects in preclinical Alzheimer's disease (AD) models related to the regulation of inhibitory neurotransmission, protection of the BBB, as well as the inhibition of inflammation and oxidative stress.
Restoration of inhibitory neurotransmission: Artemisinins have been shown to modulate the expression of GABAergic and glycinergic synaptic proteins in the APP/PS1 mouse model. The brain levels of γ2-GABAAR and gephyrin, a scaffolding protein component of inhibitory synapses, were increased in 12-month-old APP/PS1 mice that had been treated with artesunate (10 mg/kg) starting at three months of age, which was accompanied by a modest decrease in amyloid plaques [7]. Levels of the glycine receptors GlyR α2 and α3 are reduced in the hippocampus of AD mice. Artesunate (10 mg/kg) was also able to restore levels of the extrasynaptic glycinergic receptor GlyR α3 levels in 12-month-old APP/PS1 mice, without significantly affecting GlyR α2 or presynaptic GlyRs [8]. As a result, artesunate treatment may help restore slow tonic inhibition in the hippocampus, leading to a normalization of the excitatory-inhibitory balance, which is disrupted in AD [8].
Restoration of BBB integrity: Artesunate was identified in a screen to promote the expression of PICALM, a protein that is highly expressed in the brain endothelium [9]. Genetic variants in PICALM have been identified as risk factors for AD [10]. 5XFAD mice deficient in PICALM (PICALM+/-) showed a two-fold increase in PICALM expression levels in brain capillaries following two months of artesunate treatment (32 mg/kg) starting at three months of age [9]. This increase in PICALM was accompanied by a reduction in Aβ in the cortex, hippocampus, and vasculature, as well as improvements to BBB integrity, cerebral blood flow responses, and performance on behavioral and cognitive tests. These protective effects were mediated by the increase in PICALM expression on brain capillaries, since the neuroprotective effects were abolished in the absence of endothelial PICALM.
Anti-inflammatory: Artesunate has been shown to have immunomodulatory properties in a variety of contexts. In BV-2 cultured microglial cells, artesunate at 100 or 200 nM inhibited Aβ-mediated production of the inflammatory cytokines TNFα, IL-1β, and IL-6 [11]. Notably, these effects were dose dependent, as low doses (<100 nM) did not show anti-inflammatory activity, while high doses (1000 nM) had cytotoxic effects. Similarly, APP/PS1 mice treated with artesunate (5 or 10 mg/kg) for six months starting at two months of age showed a reduction in the expression of TNFα, IL-1β, and IL-6 and improved performance on the Morris water maze [11].
Mitigate mitochondrial dysfunction: Artesunate was able to protect against measures of mitochondrial dysfunction, such as altered mitochondrial membrane potential, mitochondrial fragmentation,

suppressed mitophagy, and altered dynamics, in cultured N2a neuronal and BV-2 microglial cells [11]. The suppression of mitochondrial dysfunction appeared to be a major mediator of the anti-inflammatory effect of artesunate in microglia. The restoration of mitochondrial dynamics in conjunction with a reduction in inflammatory cytokine production was also seen with artesunate *in vivo* in the APP/PS1 mouse model [11].
It should be noted that many of these protective effects were shown to be dose-dependent and possibly state-dependent, such that low doses are protective, whereas high doses of artemisinins do not exert neuroprotective effects, and instead, may be harmful. It is hypothesized that this is related to a hormetic effect, wherein low doses of a potential toxic substance produce a beneficial adaptive effect [8]. As a result, there is likely to be a defined concentration range for the neuroprotective activities of artesunate and other artemisinin derivatives. Additionally, the therapeutic concentration may vary based on the presence or absence of Aβ [11].

Traumatic brain injury and hemorrhage: POTENTIAL BENEFIT FOR MILD INJURY (Preclinical)
Artesunate has been shown to mitigate neurological injury in rodent models of traumatic brain injury and intracerebral hemorrhage. In the controlled cortical impact model, artesunate (30 mg/kg), administered one hour after craniotomy, reduced lesion volume and neuronal loss in mice [12]. This was accompanied by a reduction in neuroinflammation driven by a reduction in the nuclear localization and subsequent activation of NF-kB, as well as a reduction of NLRP3 inflammasome activation, and associated downstream effectors IL-1β and caspase-1. Additionally, artesunate protected against the loss of neurotrophin expression, including NT-3, BDNF, and GDNF, in response to neural injury. In the same model, rats treated with artesunate (100 mg/kg) showed a reduction in brain infarct size, brain water content, neuroinflammatory cytokines (TNFα, IL-1β, IL-6), and disruption to the integrity of the BBB [13]. Mechanistically, artesunate promoted the phosphorylation of Akt, which effectively blunted the trauma-related induction of GSK3β signaling. Artesunate (50 mg/kg) was also shown to reduce pro-inflammatory M1-polarized microglia, neurological deficits, hematoma volumes, and brain edema, in a hemoglobin-induced model of intracerebral hemorrhage in male rats [14]. *In vitro*, artesunate was found to reduce the viability of inflammatory M1-polarized microglia via the induction of ferroptosis [14].

However, these effects did not translate in a clinical trial testing artesunate in trauma patients with hemorrhage, although it should be noted that this study was not specifically looking at intracerebral hemorrhage, and patients with severe traumatic brain injury were excluded from the trial. The placebo-controlled study (n=83) included 54 participants who received an intravenous bolus of artesunate (2.4 mg/kg or 4.8 mg/kg) within four hours of injury [15]. The study was terminated early due to an

increase in adverse events, namely venous thromboembolic events, in the artesunate group, while no clear benefits on any of the trial outcomes, such as organ failure, were seen. The lack of benefit may have been related to an imbalance in the study population, in which those receiving artesunate had more profound shock and greater baseline deficits, suggesting that if artesunate offers benefit, it may only be in context of mild, but not moderate or severe, trauma.

APOE4 interactions: Not established.

Aging and related health concerns: Artesunate may offer some protection against a variety of pathogen-related diseases, including some forms of cancer. It also shows anti-inflammatory and anti-fibrotic effects in a wide range of preclinical models.

Types of evidence:

- 1 meta-analysis of clinical studies testing artesunate in Schistosomiasis
- 5 clinical trials for artesunate in cancer
- 1 review assessing the use of artesunate in non-malarial infectious diseases
- 1 clinical trial testing artesunate in covid-19
- 1 clinical trial testing artesunate in HIV
- Numerous laboratory studies

Lifespan: POTENTIAL BENEFIT IN YEAST (Preclinical)
Calorie restriction induces changes to mitochondrial signatures, with different effects in the acute and chronic phases [16]. In yeast, artesunate was found to mimic the delay in aging phenotypes induced by calorie restriction by replicating the mitochondrial remodeling [16]. The mechanism involves the production of nitric oxide and hydrogen peroxide to induce antioxidative networks which scavenge reactive oxygen species (ROS) and mitigate oxidative stress, leading to a change in metabolic function that promotes life extension in yeast. Artesunate can mimic this process because the artesunate-heme conjugation functionally resembles the nitric oxide-heme interaction, which is a driver of this response. It has not been established whether artesunate can replicate the benefits of calorie restriction in higher order species.

Cancer: POTENTIAL BENEFIT ESPECIALLY FOR VIRAL-ASSOCIATED CANCERS

Numerous preclinical studies indicate that artesunate has anti-cancer properties against a variety of cancer cell lines [17]. The mechanisms associated with these anti-cancer effects include the production of free radicals, cell cycle arrest, ferroptosis, apoptosis, the inhibition of angiogenesis, and the inhibition of proliferation. Additionally, artemisinins show broad anti-viral activity, and thus may benefit some viral-associated cancers. Artesunate has been tested in clinical trials for several different types of cancers, and exhibited modest efficacy in some populations. No objective responses were seen in patients with advanced solid tumors that had failed to respond to standard treatments (n=19) following treatment with intravenous artesunate (doses ranging from 8 to 45 mg/kg and days 1 and 8 of a 21-day dosing cycle) [18]. However, at the maximum tolerated dose (18 mg/kg), the plasma levels of artesunate and its active metabolites were only one-fifth of those needed to see efficacy in preclinical models, which may have contributed to the lack of response, and suggests that this dosing scheme may be ineffective for eliciting a therapeutic response.

Colorectal Cancer: Oral artesunate (200 mg/day) for 14 days was tested in patients with colorectal cancer prior to undergoing resection surgery in a randomized, placebo-controlled trial (n=23) [19]. A higher degree of tumor cell apoptosis was seen in the context of artesunate. A higher proportion of artesunate-treated patients showed survival beyond two years (91%, 95% CI 54% to 98%), relative to the placebo-treated group (57%, 95% CI 28% to 78%). Based on these results, a larger Phase 2 trial is currently being conducted testing 200 mg/day oral artesunate in patients (n=200) with Stage II/III operable colorectal cancer (NCT02633098).

Cervical Cancer: Intravaginal artesunate administered as five day treatment cycles prior to standard-of-care resection at study week 15 was tested in 29 patients with cervical intraepithelial neoplasia (CIN) 2/3 [20]. Artesunate showed efficacy in clearing both CIN2/3 lesions and human papillomavirus (HPV). Benefits were observed regardless of whether participants underwent one, two, or three treatment cycles, with histological recession occurring in >60% of participants in all dosing groups. Histologic regression to CIN1 or less was observed in 19 out of 28 (68%) evaluable subjects. However, the time to histological recession was longer in those with only one cycle (20.4 weeks) relative to those with multiple cycles (12.9 weeks). Of the 19 subjects with histological recession, nine exhibited a clearance of baseline HPV genotypes. Clearance rates were highest for those whose lesions were not associated with the strain HPV16. Based on these results, a double-blind placebo-controlled Phase 2 study is being conducted testing artesunate vaginal inserts in patients (n=78) with biopsy-proven HPV-associated CIN 2/3 (NCT04098744).

Lung Cancer: Artesunate, administered intravenously (120 mg/day from the 1st day to 8th day) was tested in combination with chemotherapy (vinorelbine and cisplatin) compared to chemotherapy alone in 120 patients with non-small cell lung cancer (NSCLC) [21]. There were no significant differences in the

short term or one year survival rates, but the addition of artesunate was associated with a higher disease control rate (88.2% vs. 72.7%), and a longer time to disease progression (24 weeks vs. 20 weeks).

Metastatic Breast Cancer: In an open label trial, 100, 150, or 200 mg/day oral artesunate for four weeks was generally well-tolerated as an add-on to their standard therapy in 23 patients with metastatic breast cancer (ARTIC M33/2) [22]. Stable disease was seen in 10 of the 15 patients evaluable for efficacy, but there were no partial or complete responses. Similarly, in a long-term add-on study including 13 of the trial participants, there were no complete or partial remissions, but disease stabilization was observed in six patients [23].

Glioblastoma: Artesunate has not yet been clinically tested in patients with glioblastoma, however, its BBB penetrance makes it a promising candidate for this indication. Preclinical studies suggest that it can work synergistically with other anti-tumor agents [24; 25].

Ischemic stroke: POTENTIAL BENEFIT (Preclinical)

Artesunate has been shown to protect against neuroinflammation and neurological injury in preclinical stroke studies, however, it has not yet been clinically tested for this indication. The vast majority of these studies utilize the middle cerebral artery occlusion (MCAO) model in rodents. In male mice, artesunate (30 mg/kg) reduced brain infarct volumes, improved functional recovery, and reduced markers of neuroinflammation, including NF-kB activation, neutrophil activation, 1ba+ activated microglia, and inflammatory cytokine production (TNFα and IL-1β) [26]. Similarly, artesunate (30 or 60 mg/kg) administered two hours prior to MCAO, reduced infarct volumes, brain edema, and neurological deficits in male rats [27]. Cell culture studies suggest the protective effects may be related to the induction of autophagy [27]. A separate study in male rats found that when artesunate was administered 10 minutes after MCAO, 80 mg/kg (i.p.) was the optimal dose to reduce infarct volume, brain edema, neuroinflammation, and neurological deficits [28].

In addition to the modulation of neuroinflammation, rodent studies suggest that artesunate can also promote post-ischemic neurogenesis in the MCAO model. In male mice, artesunate (150 mg/kg i.p.) starting immediately after reperfusion increased the number of proliferative neural progenitor cells in the subventricular zone and peri-infarct area [29; 30]. The neurogenesis effect appears to involve the inhibition of FOXO3a transcriptional activity and modulation of the PI3K/Akt signaling pathway.

The optimal potential therapeutic dose has not been established for this indication. The dose of 80 mg/kg, indicated in one study, is equivalent to the human dose of 12.9 mg/kg, which is substantially higher than the approved dose for malaria of 2.4 mg/kg (i.v.) [28], though still below the 18 mg/kg maximally tolerated dose limit observed in a clinical trial in cancer patients [18].

Rheumatoid arthritis: POTENTIAL BENEFIT (Preclinical)
Artesunate was shown to inhibit the inflammation driven migration of fibroblast-like synoviocytes derived from the synovial fluid of patients with rheumatoid arthritis [31]. The effect was superior to that of hydroxychloroquine and synergistic when combined with methotrexate. The inhibition of Akt signaling, as well as the metalloproteases, MMP-2 and MMP-2 appear to be involved. In the K/BxN mouse model of rheumatoid arthritis, artesunate (100 mg/kg i.p., twice/day) for two weeks starting at three weeks of age was able to prevent the onset of arthritis in 80% of treated mice by inhibiting germinal center B cell differentiation and autoantibody production [32]. However, it was less effective for serum transfer-induced arthritis or the inflammatory phase, suggesting that artesunate may be more effective in preventing inflammatory damage than alleviating it.
In addition to its anti-inflammatory effects, artesunate has shown evidence of reducing arthritis-related bone loss. Artesunate can inhibit the induction of RANKL and NFATc1, major transcriptional drivers of osteoclastogenesis [33]. Artesunate dose dependently decreased the production of osteoclasts following inflammatory lipopolysaccharide (LPS) stimulation in pre-osteoclastic RAW264.7 cells and suppressed ROS production in mouse bone marrow macrophages [33; 34]. The suppression of oxidative stress and induction of antioxidant programs, such as Nrf2, may drive the protection against inflammatory bone loss [33]. The protection against inflammation (LPS)-induced bone loss was also observed *in vivo* [34].

Fibrotic disease: POTENTIAL BENFIT (Preclinical)
Artesunate and other artemisinins have been shown to exert anti-fibrotic properties in a variety of different organs and model systems [35]. These studies suggest that the anti-fibrotic effects are mediated through anti-proliferative and pro-apoptotic effects in fibrogenic myofibroblast precursors, as well as the inhibition of myofibroblast differentiation and downregulation of pro-fibrotic gene expression in other cell types. The suppression of PI3K/Akt signaling appears to be one of the major molecular drivers of these effects. A better understanding of the organ distribution of artemisinin and its derivatives is needed to determine which fibrotic conditions are most likely to benefit, but thus far benefits have been seen in multiple preclinical models for kidney, liver, and lung fibrosis.

Hepatic fibrosis: In the CCl_4-induced mouse model of liver fibrosis, treatment with artesunate (50 to 200 mg/kg i.p) during the last four weeks of CCl_4, induced ferroptotic cell death in the activated pro-fibrotic hepatic stellate cells, and attenuated markers of liver fibrosis [36]. In the context of liver cirrhosis induced by CCl_4, 10% ethanol, and a high-fat diet, male rats treated with artesunate (25 mg/kg/day

intragastrically) exhibited lower levels of inflammatory cytokines (IL-6 and TNFα), steatosis, histopathological fibrosis, as well as a reduction in microbiota dysbiosis [37]. Similarly, in the CCl_4 rat model, artesunate (28.8 mg/kg/day orally) treatment was associated with a reduction in liver cytokines (IL-6 and TNFα), immune cell infiltration, and fibrous tissue hyperplasia [38]. Artesunate dampened the induction of pro-inflammatory and pro-fibrotic signaling cascades driven by the hepatic expression of TLR4, MyD88, NF-κB p65 and TGF-β1.

Renal fibrosis: In rodent models of diabetic nephropathy, treatment with artesunate and other artemisinin derivatives have been shown to improve kidney function, as evidenced by a reduction in the level of blood urea nitrogen (BUN) and proteinuria [39]. Artemisinins were also associated with a reduction in glomerular fibrosis, which may be related to the attenuation of TGF-β1 signaling and MMPs. In the unilateral ureteral obstruction model, artesunate (30 mg/kg) reduced the deposition of interstitial collagen and downregulated the expression of α-smooth muscle actin in the kidneys of male rats [40]. Artesunate restored the balance of pro- (i.e. USAG-1) and anti-fibrotic (i.e. BMP-7) gene expression, and inhibited the renal infiltration of inflammatory macrophages.

Pulmonary fibrosis: In the bleomycin-induced model of pulmonary fibrosis, the expression of pro-fibrotic genes, such as collagen-IV, MMP-2, and MMP-9, was reduced in lung fibroblasts derived from rats treated with artesunate (100 mg/kg/day i.p.) [41]. Artesunate (1 mg/kg/day i.p.) also inhibited the bleomycin-induced expression of α-smooth muscle actin, collagen-IV, and the Notch signaling pathway [42]. In the HFL-1 human fibroblast cell line, artesunate was found to inhibit fibrotic gene expression via the inhibition of MAPK signaling through Smad7 [43].

Atherosclerosis: POTENTIAL BENEFIT (Preclinical)
Artesunate has been shown to slow the progression of atherosclerosis in high-fat diet-induced rodent models via modulation of the inflammatory profile of macrophages [44]. The effects on plaque development were comparable to rosuvastatin, while the effects on arterial wall remodeling were superior [45; 46]. As a result, the combination of artesunate with rosuvastatin showed more anti-atherosclerotic potential relative to either drug alone [46]. The reductions in plaque development with artesunate were independent of effects on blood lipid levels, but rather, associated with a reduction in pro-inflammatory cytokines, such as TNFα and IL-6, stemming from the inhibition of macrophage recruitment [44; 45; 46]. Additionally, artesunate inhibited NF-kB signaling and NLRP3 inflammasome activation in arterial macrophages [5]. Artesunate shifted the balance of macrophages away from pro-inflammatory M1-like toward an anti-inflammatory M2-like profile [44]. In cultured human THP-1

monocyte-derived macrophages, pretreatment with artesunate reduced the formation of oxidized-LDL-induced foam cells, and their accumulation of cholesterol via the upregulation of ABCA1-mediated efflux [47].

Pathogen-driven disease: BENEFIT FOR MALARIA, POTENTIAL BENEFIT FOR OTHER DISEASES IS MODEST OR UNCLEAR

In preclinical studies, artemisinins have shown protection against a wide range of parasites, bacteria, viruses, and viral-related cancers [3]. In addition to being the first line recommended treatment for severe malaria, artesunate has been clinically tested in a variety of other pathogen-related diseases. For most of these studies, the preclinical benefits have not translated into clinical efficacy.

Malaria: Artesunate (i.v.) is currently the only drug for severe malaria approved by the FDA. Production of the antimalarial drug, quinidine, which is the only previously approved drug for malaria, was discontinued in 2019, at which time artesunate became the first line treatment for malaria per the guidelines of the World Health Organization. The approval by the FDA, in 2020, was based on evidence in two clinical trials (n= 1,461 and n=5,425, respectively) in which artesunate was associated with a significant reduction in malaria-related deaths, relative to quinine (Press Release).

Schistosomiasis: A meta-analysis of 24 clinical studies testing artesunate or other artemisinin derivatives alone or in combination with other agents found that artesunate (6 mg/kg once) (Relative Risk [RR]: 0.11, 95% CI 0.06 to 0.22; P < 0.001) was effective as a prophylactic agent (n=6,367) [48]. As a treatment, artesunate (4 mg/kg for 3 days) as a monotherapy was less effective relative to praziquantel (n=800), but the combination was the most effective (n=536). Since artesunate acts early in the course of infection, it is most effective for prophylaxis, and becomes increasingly less effective once the parasitic infection has been established.

Leishmaniasis: A double-blind placebo-controlled study testing 100 mg artesunate + 250 mg/12.5 mg sulfamethoxypyrazine/pyrimethamine (n=41) found that the combination had comparable efficacy to placebo [49].

CMV: In an RCT including 494 Ugandan children receiving either artesunate with amodiaquine or sulfadoxine-pyrimethamine with amodiaquine for acute malaria infection found no detectable difference in the frequency or quantity of CMV in blood across treatment arms [50]. In an uncontrolled study including six stem cell transplant recipients who received preemptive artesunate (200 mg × 2/day for 1 day, followed by 100 mg/day for 28 days) for a multidrug-resistant CMV infection, viral loads declined in two patients, but continued to grow in the other four patients [51]. Case reports suggest that artesunate may be beneficial in patients with mild CMV diseases, but ineffective in those with more advanced illness [3; 52].

Lyme: In an uncontrolled pilot trial, seven patients with Lyme borreliosis treated with artesunate (20 mg × 4/day) in combination with ceftriaxone did not experience a reduction in short-term memory problems [6].
Covid-19: Artesunate (60 mg, twice daily) was compared to the routine treatment of lopinavir/ritonavir (500 mg, twice daily) plus α-aerosolized interferon (500×10^4 U, twice daily) for ten days in patients hospitalized with Covid-19 (n=43) [53; 54]. Artesunate treatment was associated with a faster improvement of symptoms (3.33±1.91 vs. 4.84±2.19 days), faster negative seroconversion time (4.72±2.16 vs. 6.68±3.76 days), and shorter length of hospital stay (16.56±3.71 vs. 18.04±3.97 days).
HIV: Based on the finding that artesunate was able to influence T cell activation in non-human primates with simian immunodeficiency virus (SIV), oral artesunate (50 mg, twice per day) was tested in combination with highly active HIV antiretroviral therapy (HAART) in patients with HIV (n=45) for 48 weeks [55]. In contrast to the study in non-human primates, the addition of artesunate did not significantly impact levels of CD4+ or CD8+ T cells, or improve immune reconstitution. Furthermore, the addition of artesunate was associated with a reduction in the levels of some T cell populations expressing immune activation markers, relative to HAART alone, suggesting that it is not clinically beneficial in this population.

Safety: Artesunate has been safe and well-tolerated for the majority of malaria patients and those in clinical trials. Common side effects include gastrointestinal effects, dizziness, and fever. Rare serious effects include liver injury, kidney injury, and hemolytic anemia.

Types of evidence:

- 1 meta-analysis or systematic reviews
- 5 clinical trials for artesunate in cancer
- 1 review assessing the use of artesunate in non-malarial infectious diseases
- 1 clinical trial testing artesunate in covid-19
- 1 clinical trial testing artesunate in HIV
- 1 clinical trial testing artesunate in traumatic hemorrhage
- Numerous laboratory studies

Artesunate has been used by millions of malaria patients without severe side effects [15]. Artesunate (i.v.) is approved by the FDA and is recommended by the World Health Organization as the first line treatment for severe malaria. According to the FDA prescribing label, the most common severe adverse

reactions (>2%) in patients with severe malaria include acute renal failure requiring dialysis, hemoglobinuria, and jaundice. Additional common adverse events include anemia, increased liver transaminases, thrombocytopenia, and hyperbilirubinemia (Medscape).

The FDA prescribing label includes a warning for post-treatment hemolytic anemia. This rare severe adverse event occurs with a delay, usually around 7 to 30 days after the initiation of artemisinin-based therapy [56]. The exact mechanism driving this adverse event is not fully understood, but is thought to be related to the process of pitting, in which dead parasites are removed from red blood cells in the spleen. These previously infected cells have lower structural integrity and a shorter lifespan. Additional mechanisms include the production of anti-drug autoantibodies and the destruction of healthy uninfected red blood cells.

A clinical trial testing intravenous artesunate (2.4 mg/kg or 4.8 mg/kg i.v.) in patients with traumatic hemorrhage (n=83) was terminated for safety concerns stemming from an increased incidence of venous thromboembolic events in participants assigned to artesunate of 17% (9/54) relative to 3% (1/29) for placebo (RR: 4.8, 95% CI 0.6 to 36.3; p = 0.078) [15]. Baseline differences in the artesunate-treated group in terms of severity of injury and rates of early thromboprophylaxis may have contributed to this outcome. There is preclinical evidence to suggest that artesunate inhibits thrombus formation in cultured platelets [57], and thus far thromboembolic events have not been observed in metastatic breast cancer patients, who are known to be at high risk for these events, with long-term (37 month) artesunate treatment [23].

Oral artesunate is used for uncomplicated malaria in combination with another antimalarial agent (MSF). Common side effects include gastrointestinal symptoms and dizziness.

Oral artesunate has also been tested in clinical trials for a variety of other indications.
In patients with metastatic breast cancer (n=13) treatment with 50, 100, or 200 mg/day oral artesunate on a compassionate care basis for up to 37 months was not associated with major safety concerns [23]. There were no grade ≥ 2 adverse events that were certainly or probably related to artesunate. There were no clinically meaningful changes in liver enzymes, heart rate, blood pressure, nor signs of QTc prolongation or thromboembolism.
In patients (n=23) with colorectal cancer treated with 200 mg/day oral artesunate for 14 days, two patients who were borderline at the lower weight limit for study inclusion experienced grade 3 leukopenia [19]. One patient also reported nausea. Otherwise, it was generally well-tolerated.

In HIV-positive patients taking 50 mg artesunate tablets twice daily in combination with anti-retroviral therapy for 48 weeks, there were no severe adverse events or reactions [55]. However, absolute lymphocyte counts were lower relative to participants taking anti-retrovirals alone. Two participants dropped out due to the aggravation of insomnia and fatigue, and one participant experienced moderate anemia, accompanied by a marked increase in reticulocytes.
There were no significant differences in the rates of adverse events between patients with Covid-19 receiving artesunate (60 mg, twice a day for 10 days) and those receiving the standard of care of (lopinavir/ritonavir 500 mg and interferon 500 $\times 10^4$ U, twice a day for 10 days) [53].

Drug interactions: According to Drugs.com, there are 3 major drug interactions and 89 moderate interactions with artesunate. Major interactions include the anti-cancer medication adagrasib, the migraine medication atogepant, and the irritable bowel syndrome medication eluxadoline. The FDA label mentions drug interactions with the antiretrovirals nevirapine or ritonavir, as well as with strong UGT enzyme inducers, such as rifampin, carbamazepine, and phenytoin.

Sources and dosing:

The recommended dose for severe malaria is 2.4 mg/kg administered intravenously (as a slow bolus over 1-2 minutes) at 0 hours, 12 hours, and 24 hours, and thereafter administered once daily until the patient is able to tolerate oral antimalarial therapy. The FDA approved formulation of injectable artesunate for severe malaria is manufactured by Amivas, LLC. For uncomplicated malaria, oral artesunate is administered in combination with another antimalarial drug, typically amodiaquine, and the dosage is based on weight (MSF). For individuals ≥36 kilograms, the oral dose is 200 mg artesunate (+ 540 amodiaquine) daily for three days. Artesunate has not been approved for use in other indications. Potential modest efficacy was seen in some pilot clinical trials for some cancers at an oral dose of 200 mg/day. Potentially therapeutic doses or administration routes for CNS indications have not yet been established.

Research underway:

According to Clinicaltrials.gov, there are currently 28 active clinical trials testing artesunate. These include trials for severe malaria, HIV-negative anal high grade squamous intraepithelial lesions, high grade vulvar intraepithelial neoplasia (HSIL VIN2/3), cervical intraepithelial neoplasia (CIN2/3), colorectal cancer, Covid-19, idiopathic pulmonary fibrosis, Crohn's disease, and Friederich's ataxia.

Search terms:

Pubmed, Google: Artesunate

- Alzheimer's disease, neurodegeneration, cognition, aging, lifespan, cancer, fibrosis, clinical trial, safety

Websites visited for Artesunate:

- Clinicaltrials.gov
- Drugs.com
- WebMD.com
- PubChem
- DrugBank.ca

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