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COMPLEMENTARY AND ALTERNATIVE MEDICINE (S KOLASINSKI, SECTION EDITOR)

Artemisinins—a Promising New Treatment for Systemic Lupus Erythematosus: a Descriptive Review

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Abstract

Purpose of Review Systemic lupus erythematosus (SLE) is a complex, potentially fatal autoimmune disease with no complete cure. Current treatments for SLE are limited by suboptimal efficacy and increased risk of infections and malignancies, and cannot meet the clinical demands of patients with SLE. Artemisinin and its derivatives (artemisinins), a new class of anti-malarial drugs, have recently been reported to have an immunosuppressive effect on lupus patients. In this review, we evaluate the therapeutic properties and potential mechanisms of artemisinins for the treatment of SLE.

Recent Findings Both clinical and animal studies suggest that artemisinins have potential beneficial effects for SLE. The beneficial effects associated with artemisinin treatment include improving symptoms, reducing level of antibodies and proteinuria, ameliorating renal damage, and diminishing the dosage of prednisone use. Animal studies suggest that mechanisms of action of artemisinins may include regulating T cell subsets, inhibiting activation of B cells and production of inflammatory cytokines, as well as blocking the NF-κB signal transduction pathway, thus playing a role in anti-inflammation and immunomodulation.

Summary Artemisinin family drugs are a promising potential new medication that may challenge the current treatment paradigms available for SLE.

Keywords Systemic lupus erythematosus · Lupus nephritis · Anti-malarial drug · Artemisinin · Treatment · Artemisinin derivatives (Artemisinins)

Introduction

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease with potential lethality, which is incurable and requires long-term treatment [1]. Current therapeutic approaches cannot meet the clinical demands of patients with SLE, and are limited by suboptimal efficacy and increased risk of infections and malignancies [2].

For more than 50 years, anti-malarial drugs have been used extensively as a background medication for SLE, especially for skin and joint symptoms [3, 4]. Although these drugs are considered generally safe and cost effective, the side effects of retinopathy and neuromyotoxicity, and suboptimal efficacy for treating lupus organ damage still limit their application [5, 6].

Recently, artemisinins, a new family of anti-malarial drugs, have increasingly been reported to exert an immunosuppressive effect on lupus. Artemisinin was first discovered by Chinese scientists in 1972, extracted from the plant *Artemisia annua L.* (qing hao), a traditional Chinese herbal medicine that has been used to treat malaria for more than 2000 years in China [7]. Unlike all other known anti-malarial drugs, artemisinin is a sesquiterpene lactone containing peroxide bridge [8••]. Subsequently, a series of artemisinin derivatives with higher bioactivity or solubility were synthesized by binding new groups to the parent structure of artemisinin, including dihydroartemisinin, artemether, artesunate, and arteether [9]. The artemisinin family drugs (artemisinins) are currently considered by the

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World Health Organization to be the most effective drugs for the treatment of cerebral malaria and chloroquine-resistant falciparum malaria, and artemisinin-based combination therapy is currently recommended as the first choice for the treatment of malaria [10].

Studies have demonstrated a variety of other pharmacological actions of artesmisinins beyond their antimalarial effects. It has been found that artemisinin family drugs also have antiviral [11, 12], antibacterial [13] and antifungal effects [14], anti-tissue fibrosis [15], and anti-inflammatory [16] as well as complex immunosuppressive effects [17]. They can even inhibit tumor growth and induce tumor cell death [18]. Similar to other anti-malarial drugs, such as hydroxychloroquine (HCQ) and chloroquine (CQ) [4], artemisinin derivatives also show therapeutic effects for SLE, as well as rheumatoid arthritis [19•, 20–22], dermatomyositis [23, 24], and other immune diseases [25]. While HCQ and CQ have potential adverse effects of severe and irreversible retinopathy and neuromyotoxicity, artemisinin drugs have been used in the treatment of millions of malarial patients without any serious side effects [26]. Thus, they may be considered a kind of safe and promising new drugs for SLE.

In this paper, we review the clinical efficacy of artemisinin family drugs in patients with lupus and the proposed immunological mechanisms of artemisinins based on experimental studies in lupus mouse models. This review of the therapeutic properties and potential mechanisms of artemisinins for SLE may challenge the current treatment paradigms available for SLE. To our knowledge, this is the first comprehensive review of current available evidence on the clinical effects and potential mechanisms of artemisinins for SLE.

Literature Survey

To identify studies for inclusion in this qualitative review, a comprehensive literature search was conducted on two English and four Chinese biomedical databases from inception through February 2018. These databases included PubMed, Springer, Chinese National Knowledge Infrastructure, Chongqing VIP, WanFang Med Online, and Chinese Biomedical Databases. Searches were limited to studies in English and Chinese. The following terms were used in the search: "artemisinin," "artemisinins," "artesunate," "dihydroartemisinin," "artemether," "lupus," "systemic lupus erythematosus," "lupus nephritis," "mechanism," "effect," "clinical trial," "experimental study," and "animal model." We also screened the reference lists of selected studies for additional publications.

The Role of Artemisinin Derivatives for Patients With SLE

Table 1 summarizes the evidence reviewed according to types of studies. Five unique clinical studies in seven articles published from 1996 to 2011 were ultimately included [27–33]. Of five clinical trials investigating artemisinin conducted in China, three were randomized controlled trials (RCT) and two were non-randomized comparative studies. Participants met 1982 ACR criteria for classification of SLE in all five studies. Of 252 patients involved, 228 were female. The average age of the patients ranged from 23 to 44 years, and the average disease duration was 11 to 46 months. Among these studies, one trial used artemisinin, while the others used artesunate, and the course of treatment ranged from 15 days to 3 years. The treatment interventions in the three RCTs combined artemisinins with prednisone, Lingdan tablet, or cordyceps sinensis powder, while control interventions included prednisone, tripterygium tablet, or Baoshenkang tablet.

The main clinical outcome was the total effectiveness rate, which assessed overall lupus disease condition, including fever, skin damage, joint pain, organ damage, and immunology and laboratory indicators, according to 1991 Chinese disease diagnosis and evaluation criteria [34].The total effectiveness rate (%) was calculated as the quotient of the number of improved patients divided by the total number of the patients. It was based on the number of patients in each of the following categories: "Significant improvement" (symptoms and disease activity index improved significantly); "Improvement" (symptoms and disease activity index improved); and "Not cured" (symptoms and disease activity index not improved).

An early randomized controlled study of 45 patients with SLE administered artesunate tablet (50 mg, twice a day) combined with Lingdan tablet and prednisone (0.25–0.8 mg/kg/day) for 3 months [27]. The patients in the control group were only given prednisone (0.8–1.25 mg/kg/day). Results showed that treatments reduced disease activity and ameliorated symptoms including fever, joint pain, erythema, rashes, and hair loss. The clinical effectiveness of the artesunate combination therapy was significantly better than that of the prednisone group. Artesunate combination therapy also resulted in significant reduction in 24-h urinary protein, erythrocyte sedimentation rate, and prednisone doses. Compared with the control group, artesunate combination treatment also led to increased CD3 and CD4 T lymphocyte count, ratio of CD4/CD8 T lymphocytes, and elevated activity of IL-2 cytokine, and decreased level of soluble interleukin-2 receptor (sIL-2R). The study concluded that artesunate and Lingdan tablets may regulate the immune system in a bidirectional manner to balance the immune function of patients with SLE by reducing the level of sIL-2R, and enhancing T lymphocyte function and IL-2 activity [28, 29].

Table 1 Clinical studies of artemisinins in systemic lupus erythematosus

Source study design [Ref]	Diagnostic criteria	*N* (female %)	Mean age (year)	Disease duration (months)	Intervention	Controls	Finding
Zhong et al. 1999, 2002, 2003; RCT [27–29]	ACR 1982 criteria for classification of SLE	45 (89%)	29	41	Artesunate tablet, 50 mg, twice a day, Lingdan tablet (ingredients: *Artemisia annua*, Mudanpi, Gentiana, turtle, buffalo horn, Rehmannia, Licorice, Scrophularia), 0.5 g × 5, three times a day, and prednisone, 0.25–0.8 mg/kg, once a day. For 3 months	Prednisone 0.8–1.25 mg/kg, once a day. For 3 months	Total effectiveness rates s 24 h urine protein s Prednisone dose s Clinical symptoms (Fever, joint pain, erythema, mucosal damage, hair loss, fatigue, Raynaud's, loss of vision) ns ↑CD_3, CD_4, $CD4/CD_8$, IL-2 s, ↓sIL-2R s ↓CD_8 ns
Lu, 2002; RCT [30]	ACR 1982 criteria for classification of SLE, and nephritis	61 (93%)	44	11	Artemisinin powder, 0.2 g, three times a day, cordyceps powder, 1 g, three times a day. For 3 years	Tripterygium glycosides tablet, 1 mg/kg, three times a day, Baoshenkang tablet, 50 mg, three times a day. For 3 years	Total effective rate s 24 h urine protein s ↓BUN, SCr, ↑CCr s ↑C_3, ↓β2-MG s ↑Alb ns
Huan, 2011; RCT [31]	ACR 1982 criteria for classification of SLE, and nephritis	60 (92%)	29	46	class I/ class II: artesunate tablet, 50 mg, twice a day; class III: artesunate tablet, 50 mg, twice a day, and prednisone 0.5 mg/kg, once a day. For 8 weeks.	class I/class II: tripterygium glycosides tablet, 10 mg, three times a day; class III: tripterygium glycosides tablet, 10 mg, three times a day, and prednisone 0.5 mg/kg, once a day. For 8 weeks.	Total effectiveness rates s 24 h urine protein s ↓ESR, CD_8^+, ↑IL-2, C_4 s ↓dsDNA, IgG, ↑C_3, CD_3^+, CD_4^+ ns
Yu, 1997, NRS (before and after trial) [32]	ACR 1982 criteria for classification of SLE	56 (86%)	31	36	SLE: artesunate 60 mg/d, intravenous injection, once a day, glucocorticoid not changed; DLE, SCLE: artesunate 60 mg/d, intravenous injection, once a day, copper sulfate zinc cream. 15 days a course, 1–4 courses	NR	Improvement in clinical symptoms (skin damage, fever, joint pain, light sensitive, hair loss) Improving ↓ANA, dsDNA ESR, IgG, IgA, ↑C_3,
Yu, 1996, NRS (before and after trial) [33]	ACR 1982 criteria for classification of SLE	30 (93%)	23	36	Artesunate 60 mg/d, intravenous injection, once a day, glucocorticoid not changed, 15 days a course, 1–4 courses	NR	Improvement in clinical symptoms (erythema, joint pain, fever, light sensitive, hair loss, Raynaud's) Improving ↓ESR, IgG, IgA, ↑C_3

SLE systemic lupus erythematosus, *DLE* discoid lupus erythematosus, *SCLE* subacute cutaneous lupus erythematosus, *Ref* reference, *RCT* randomized controlled trial, *NRS* non-randomized controlled study, *NR* no relevant, *ESR* erythrocyte sedimentation rate, *s* significant, *ns* no significant

Total effectiveness rates assesse overall lupus disease score, including fever, skin damage, joint pain, and immunology and laboratory indicators, according to 1991 Chinese disease diagnosis and efficacy criteria

In the second randomized study [30], 61 patients with inactive lupus nephritis were randomly assigned into two groups, each receiving 3 years of treatment. Artemisinin (0.2 g, three times a day) and cordyceps were given in the treatment group, and tripterygium glycosides tablet and Baoshenkang tablet were given in the control group. Compared with the control group, the total effectiveness rate of the treatment group was significantly improved (83.9 vs. 50.0%). The 24-h urine protein content, the creatinine clearance rate, and level of complement 3 in the treatment group were also significantly improved compared to the control group. The study concluded that artemisinin and cordyceps may delay the recurrence of lupus nephritis, protect renal function, and improve the quality of life of patients with SLE.

Similar findings of improvement in renal function and the immune system from artesunate were reported in another randomized controlled study of 60 lupus nephritis patients [31]. In the 2-month randomized trial, patients with class I and class II lupus nephritis were treated with artesunate (50 mg, twice a day), and the control group was treated with tripterygium glycosides tablet (10 mg, three times a day). Patients with class III lupus nephritis were treated with prednisone (0.5 mg/kg/day) plus artesunate, compared to prednisone (0.5 mg/kg/day) plus tripterygium glycosides tablet. The overall results showed that the artesunate group had decreased 24-h urine protein and erythrocyte sedimentation rate, improved lupus nephritis symptoms, immunological indexes, and total effectiveness rate compare to the tripterygium glycosides group.

The two non-randomized comparative studies used intravenous injection of artesunate (60 mg/day) with prednisone in patients with SLE, discoid lupus erythematosus (DLE), and subacute cutaneous lupus erythematosus (SCLE) [32, 33]. After 2 to 8 weeks of treatment, the 30 patients in the first study showed improvement in clinical symptoms including skin damage, joint pain, light allergy, hair loss, and fever. The second study was conducted to further investigate the effect of artesunate on skin damage in 16 DLE and 10 SCLE patients. After 2 weeks of treatment with artesunate and copper sulfate zinc cream, the total effective rates for the DLE and SCLE groups were 94 and 90% respectively. These studies concluded artesunate could alleviate light allergy and skin damage, improve suppressor T cell activity, and inhibit the formation of circulating immune complexes in patients with lupus.

Overall, these clinical studies demonstrated that artemisinins have the potential to improve clinical symptoms of SLE, decrease antibody and creatinine levels, erythrocyte sedimentation rate, and urinary protein, as well as increase the level of complement. Long-term application of artemisinins may help to alleviate renal lesions and prevent the recurrence of lupus nephritis. In next section, we will review artemisinin derivatives in animal experiments to reveal the potential anti-inflammatory role and immunosuppressive effects mechanisms of artemisinins in SLE.

Experimental Study of Artemisinin Derivatives in Lupus Mouse Models

The therapeutic mechanisms of artemisinins in lupus mice involve different pathways of the immune system, including effects on various cytokines, immune cells, and signal transduction pathways.

Table 2 describes the characteristics of the 19 animal studies that have investigated the potential immune mechanisms of artemisinin derivatives for renal pathology and disease activity in SLE [35, 36, 37••, 38–43, 44•, 45–52, 53].

Three well-established murine models of lupus (MRL/lpr, NZBW/F1, and BXSB mouse strains [54, 55]) were used in 12 of the 19 studies, which spontaneously develop human lupus-like disease. Seven studies used lupus models obtained by inducing BALB/C, B6D2F1, or KM mice into lupus-like mice. The durations of treatment ranged from 1 to 18 weeks. Four artemisinin derivatives were observed in the experiments, including artemisinin, dihydroartemisinin (DHA), artesunate, and a type of artemether named SM934. Control treatments in the experiments were varied, including prednisone, cyclophosphamide, tripterygium, and hydroxychloroquine.

Artemisinin

Aretmisinin is the first compound that was derived from *Artemisia annua*. Three studies have investigated the anti-inflammatory actions of artemisinin on SLE using B6D2F1 and KM lupus mouse models. Of the three studies, two were found that treatment with oral artemisinin (150 and 5.55 mg/kg/day) decreased serum levels of tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6), and inhibited the expression of nuclear factor-κB protein 65(NF-κB p65) and transforming growth factor-β1(TGF-β1) mRNA in the renal tissues of lupus mice [35, 37••]. In addition, artemisinin treatment was found to significantly increase the expression of P300/CBP protein in renal tissue and glucocorticoid receptors α (GRα) mRNA in peripheral blood mononuclear cell (PBMCs) compared with prednisone treatment in lupus nephritis mice [36]. Using the KM mice of lupus models, the study also found artemisinin (5.55 mg/kg/day) combined with low-dose HCQ therapy exerted renal protective effects by upregulating expression of Krüppel-like factor 15(KLF15) mRNA and downregulating NF-κB mRNA [37••].

Dihydroartemisinin

Dihydroartemisinin, as a metabolite of artemisinin, is considered to have a stronger effect than artemisinin in antimalarial treatment. Of the seven studies that evaluated dihydroartemisinin as the primary intervention on lupus mice, four used the BXSB mouse model (5–125 mg/kg/

Table 2 Study characteristics of animal experiments in systemic lupus erythematosus ($N = 19$)

Study [Ref]	Animal model	Artemisinins dose	Control	Duration (week)	Outcome	Target
Artemisinin ($n = 3$)						
Wu, et al.2010 [35]	B6D2F1 mice	Artemisinin 150 mg/kg/day	Hydroxychloroquine	8	Urine protein Pathological renal lesion	↓TNF-α, IL-6 in serum; ↓ NF-κBp65 protein, NF-κB and TGF-β1 mRNA expression in renal tissue
Wu, et al.2012 [36]	B6D2F1 mice	Artemisinin 150 mg/kg/day	Prednisone	8	ND	↑P300/CBP protein in renal tissue; ↑ GRβ mRNA in PBMCs ↓ GRα mRNA in PBMCs
Liang, et al.2018 [37••]	KM mice	Artemisinin 5.55 mg/kg/day	Prednisone	8	Urine protein, Serum creatinine, urea nitrogen, ANA, dsDNA,	↓ IFN-ɤ, TNF-α, TGF-β1 in serum; ↑ KLF15 mRNA in renal tissue; ↓ NF-κB mRNA in renal tissue
Dihydroarteannuin (DHA, $n = 7$)						
Xu, et al.2002 [38]	M BXSB mice	DHA 12.5, 25, 50 mg/kg/day	Prednisone	6.4	Urine protein	↑ CD4 and CD8 T cell in spleen, ↓ B cell in spleen
Dong, et al.2003 [39]	M BXSB mice	DHA 5, 25, 125 mg/kg/day	Vehicle	1	dsDNA, pathological renal lesions	↓TNF-α in serum
Dong, et al.2003 [40]	M BXSB mice	DHA 5, 25, 125 mg/kg/day	Vehicle	1.4	Pathological renal lesions	↓ NF-κBp65 protein expression in renal tissue ↓ NF-κB activation in renal tissue
Li, et al.2006 [41]	M BXSB mice	DHA 5, 25, 125 mg/kg/day	Vehicle	1.4	ND	↓TNF-α in peritoneal macrophages (in vivo and in vitro) ↓ NF-κBp65 translocation in peritoneal macrophages (in vitro); ↓ IκB-α protein in renal tissue
Huang, et al. 2014 [42]	F MRL/lpr mice	DHA	Vehicle	ND	ND	↓TLR4 protein, ↓IRF3 protein and phosphorylation, ↓IFN-β gene and protein. in spleen cells (in vitro)
You, et al.2014 [43]	F MRL/lpr mice	DHA 25, 50, 100 mg/kg/day	Prednisone	8	Urine protein, Serum creatinine, urea nitrogen, Pathological renal lesion	↓NF-κBp65 protein and mRNA in renal cortex ↓ FKN protein and mRNA in renal cortex
Huang, et al.2015 [44•]	MRL/lpr mice	DHA 25, 50, 100 mg/kg/day	Prednisone	12	Pathological renal lesion	↑SIGIRR expression in renal tissue and in HK-2 cells (in vivo and in vitro) ↓ IL-6 in HK-2 cells (in vitro) ↓ CCL2 in HK-2 cells (in vitro)
Artesunate ($n = 6$)						
Zhu, et al.2003 [45]	BALB/C Mice	Artesunate 25 mg/kg/day	Tripterygium	12	Pathological renal lesion	↓IL-6 in kidney
Zhu, et al.2004 [46]	BALB/C mice	Artesunate 25 mg/kg day	Tripterygium	12	ND	↓IL-6 in serum ↑TGF-β in serum
Jin, et al.2007 [47]	MRL/lpr mice	Artesunate 125 mg/kg/day	Cyclophosphamide	16	Pathological renal lesion	↓VEGF protein and mRNA in kidney
Lin, et al.2008 [48]	BALB/C mice	Artesunate 0.42, 0.84, 1.68 mg/day	Prednisone	1.1	ND	↑CD4, CD8 T cells in peripheral blood

Table 2 (continued)

Study [Ref]	Animal model	Artemisinins dose	Control	Duration (week)	Outcome	Target
Jin, et al.2009 [49]	F MRL/lpr mice	Artesunate 125 mg/kg/day	Cyclophosphamide	16	Urine protein, Serum creatinine ANA, dsDNA, Pathological renal lesion	↓MCP-1 in serum, urine and kidney ↓BAFF protein and mRNA in spleen
Wang, et al.2010 [50]	F MRL/lpr mice	Artesunate 50 mg/kg/day	Vehicle	16	Urine protein, Serum creatinine	↓ ICAM-1 in serum, in renal tissue, on peripheral blood lymphocytes
SM934 ($n = 3$)						
Hou, et al.2011 [51]	F MRL/lpr mice	SM934 2.5, 10 mg/kg/day	Prednisone	8	Urine protein, Pathological renal lesion	↓IFN-γ in serum; ↓IFN-γ and IL-17 in splenocytes (in vitro); ↓Th1, Th17 cells in splenocyte (ex vivo) ↓ STAT-1,-3,-5 in splenocyte (ex vivo)
Hou, et al.2012 [52]	NZB/W mice	SM934 1, 3, 10 mg/kg/day	Prednisone	12	Urine protein, pathological renal lesion	↓IL-17 in serum; ↑IL-4 in serum; ↑IL-10 in serum and from macrophages (in vivo and in vitro) ↑ CD4+ T cell apoptosis ↑ regulatory T cell accumulation
Wu, et al.2016 [53••]	F MRL/lpr mice	SM934 2.5, 5, 10 mg/kg/day	Prednisone	18	Urine protein, serum urea nitrogen Pathological renal lesion	↓IL-6, IL-10; ↓ activated B cell and plasma cell (in vitro); ↓TLR7 and TLR9 mRNA in splenocyte (ex vivo) ↓MyD88, NF-κB phosphorylation

ND no data, *BAFF* B cell activating factor, *CCL2* chemokine (C-C motif) ligand 2, *FKN* fractalkine *GRα* glucocorticoid receptors alpha, *GRβ* glucocorticoid receptors beta, *ICAM-1* intercellular adhesion molecule 1, *IFN-β* interferon beta, *IFN-γ* interferon gamma, *IκB-α* nuclear factor of kappa light polypeptide gene enhancer in B cells inhibitor alpha, *IL-4* interleukin 4, *IL-6* interleukin 6, *IL-10* interleukin 10, *IL-17* interleukin 17, *IRF3* interferon regulatory factor 3, *KLF15* Krüppel-like factor 15, *MCP-1* monocyte chemoattractant protein 1, *MyD88* myeloid differentiation primary response 88, *NF-κB* nuclear factor kappa-light-chain-enhancer of activated B cells, *P300* EP300 or E1A binding protein p300, *CBP* CREB binding protein, *SIGIRR* single Ig IL-1-related receptor, *STAT-1,-3,-5* signal transducer and activator of transcription 1,3,5, *TGF-β1* transforming growth factor beta 1, *Th1* T helper 1 cells, *Th17* T helper 17 cells, *TLR4* Toll-like receptor 4, *TLR7* Toll-like receptor 7, *TLR9* Toll-like receptor 9, *TNF-α* tumor necrosis factor alpha, *VEGF* vascular endothelial growth factor

day). Similar to artemisinin, dihydroartemisinin was found to improve lupus symptoms in BXSB mice by reducing serum level of TNF-α and its production from macrophages [39, 41]. Dihydroartemisinin treatment also led to significantly increased numbers of CD4 and CD8 T cells and decreased number of B cells in spleen. This suggests that dihydroartemisinin may inhibit the activation of B cells and antibody production [38].These experiments also showed that dihydroartemisinin suppressed the expression and nuclear translocation of NF-κB p65 in BXSB mice, thereby preventing the inflammatory response and alleviating renal pathology [40, 41]. Three additional studies using the MRL/lpr mouse model of SLE further indicated that dihydroartemisinin (25–100 mg/kg/day) blocked signaling in the NF-κB pathway by regulating the upstream and downstream gene expression in this signaling pathway [42, 43, 44•]. Therefore, results from these seven studies suggested that dihydroartemisinin may possess promising protective effects for lupus nephritis.

Artesunate

The immunosuppressive mechanism of artesunate on lupus was investigated in six studies using MRL/lpr and BALB/C lupus mouse models. Two studies showed that artesunate (25 mg/kg/day) reduced levels of IL-6 and TGF-β in BALB/C lupus mice significantly [45, 46]. Subsequently, evidence also showed that artesunate treatment (0.42–1.68 mg/day) ameliorated the progression of disease by regulating the proliferation of T cell subsets in BALB/C mice, which was similar to the therapeutic effect of dihydroartemisinin [38, 48]. Moreover, treatment with artesunate (50 and 125 mg/kg/day) could inhibit the expression of pro-inflammatory cytokines in MRL/lpr lupus mice, such as vascular endothelial growth factor (VEGF), monocyte chemotactic protein-1 (MCP-1), B cell-activating factor (BAFF), and intercellular cell adhesion molecule-1(ICAM-1) [47, 49, 50].

SM934

SM934 is a type of artemether, a water-soluble artemisinin derivative. Three studies have explored the therapeutic effects and immunosuppressive mechanisms of SM934 in lupus mice, of which two studies were in MRL/lpr mice [51, 53••] and one was in NZB/W mice [52]. In MRL/lpr mice, the therapeutic effects of SM934 (2.5–10 mg/kg/day) were characterized by decreasing the serum level of pathogenic cytokines interferon- (IFN-), interleukin-10(IL-10), and IL-6 [51, 53••]. SM934 treatment also suppressed Th1 and Th17 cell development, while elevating the proportion of T regulatory cells (Treg cells) [51]. Further investigations revealed that SM934 significantly inhibited the excessive activation of signal transducer and activator of transcription1, 3, 5 (STAT1, STAT3, and STAT5) [51]. In addition, SM934 impeded the B cell activation by downregulating Toll-like receptor 7/9 (TLR7/9) and myeloid differentiation primary response 88(MyD88) expression and NF-κB phosphorylation, similar to the finding that DHA inhibits activation of TLR4 [44•, 53••]. The pathogenesis in NZB/W mice is different from that in MRL/lpr mice. In NZB/W mice, SM934 treatment (1–10 mg/kg/day) promoted IL-10 production from macrophages and yielded increased serum levels of IL-10, which was inconsistent with results in MRL/lpr mice [52].

Taken together, these studies in lupus mouse models found similar therapeutic effects of artemisinin derivatives compared to the control groups, which included improved symptoms, reduction of urinary protein, and alleviation of pathological renal lesions as well as improved survival rates. The mechanisms of action of artemisinins that regulate the immune system may include inhibition of B cell activation, production of inflammatory cytokines, and NF-κB signal transduction as well as the reduction of serum anti-dsDNA.

In addition to the animal model, artesunate was found to significantly inhibit macrophage migration inhibitory factor (MIF) production in human umbilical vein endothelial cells (HUVEc) of SLE patients. Therefore, artesunate may have therapeutic potential for SLE-associated atherosclerosis [56••].

Safety and Adverse Effects

There are no serious side effects reported during artemisinins treatment for malaria patients despite mild side effects including nausea, vomiting, and diarrhea [57]. A meta-analysis of clinical trials concluded artemisinin drugs are considered as safe and well tolerated with no difference among the various derivatives [58•]. Results of one study in Mozambique reported hearing loss in malaria patients treated with oral artemether-lumefantrine [59], but a subsequent study showed no evidence of audiotoxicity [60]. With rectal administration of an artesunate suppository, 6% patients experienced tenesmus, elevated serum transaminases, and decreased reticulocytes and neutrophils [61]. In addition, there have been few cases that reported on the clinical use of artemisinins in children and pregnant women. Thus, there are insufficient data to indicate toxicity to children and fetuses [62, 63]. One of the main potential benefits of using artemisinins for SLE patients is for reduced toxicity of treatment.

Unlike most immunosuppressants, artemisinins have no serious side effects reported during treatment. It has been shown that liver function, renal function, and routine blood tests remain normal in most patients treated with artesunate for various indications [26, 64•], suggesting that the agent will also present minimal risk to patients with SLE. In the clinical trials of artemisinins for SLE, reticulocyte count decrease was

observed in three patients treated with intravenous artesunate. However, the reticulocyte counts returned to normal after 2 weeks of discontinuation of artesunate [32, 33]. Therefore, the side effects observed in association with artemisinins treatment include a decrease in reticulocyte count. As a result, it has been suggested that routine blood testing is necessary in the use of artemisinins for lupus.

Conclusion

Artemisinin derivatives have attracted increasing attention for their potential benefits for lupus in recent decades and have prompted a growing number of related studies. The evidence compiled in this review demonstrates that artemisinin family drugs are a promising new safe and effective therapy for patients with SLE, especially for lupus nephritis and skin damage, which complements the current demands of lupus treatment.

Both clinical and animal studies suggest that artemisinins have potential beneficial effects for lupus. The beneficial effects associated with artemisinin use include improved symptoms, reduced level of antibodies and proteinuria, less renal damage, and reduced prednisone use. Animal studies suggest that mechanisms of action of artemisinins may include regulating T cell subsets, inhibiting activation of B cells and production of inflammatory cytokines, as well as blocking the NF-κB signal transduction pathway, thus playing a role of anti-inflammation and immunomodulation. In summary, beyond their anti-malarial effects, artemisinin derivatives have many pharmacological properties, particularly immunomodulatory actions that may aid in the treatment of SLE. Future rigorous study is warranted to support the widespread clinical application of the treatment and to further elucidate the mechanisms underlying their therapeutic effects.

Despite accumulating evidence on the use of artemisinins, the literature on its potential as a treatment for lupus erythematosus is still insufficient, especially due to the lack of large randomized controlled trials. Further evaluation of efficacy requires more scientific and rigorously designed clinical trials. In the future, investigation of the mechanism of its pharmacological actions may also facilitate the discovery of novel drug targets to treat SLE.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

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