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Derivatives of Artemisinin in Systemic Lupus Erythematosus

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Abstract. Systemic lupus erythematosus (SLE) a chronic diffuse connective tissue disease caused primarily by abnormal activation of the immune system, which attacks its own tissues. It is the most common in women of reproductive age. The exact cause of SLE is unknown, currently, people thought that the development of SLE may be related to genetics, environment and oestrogen. Exacerbations of SLE can be triggered by sun exposure, use of specific drugs, infections, and oral oestrogen use. Unfortunately, SLE cannot be cured completely and long-term remission can only be achieved after standard treatment. Thus, the priority now is to find effective therapeutic drugs and a systematic treatment plan. Contemporary clinical treatments for therapeutic use are classified as non-steroidal anti-inflammatory drugs (NSAIDs), anti-malarial drugs, immunosuppressive drugs and corticosteroids. After searching the literature from pubmed and medical innovation of China, I found that the anti-malarial drugs are one of the basic drugs in the treatment of SLE, controlling the rash and reducing photosensitivity, as well as helping to maintain the stability of SLE and reduce the use of glucocorticoids. This paper introduced some newly found curing pathway taking dihydroartemisinin (DHA) and β-aminoarteether maleate (SM934) as the drug treatment, which both show a good immunosuppressive activity and low toxicity in mouse experiments to act as an immunosuppressant immunosuppressant mouse experiments used as adjuvant therapy.

Keywords: Derivatives of Artemisinin, Systemic Lupus Erythematosus, Immunomodulatory Effect, Dihydroartemisinin, SM934.

1. Introduction

Although patients with SLE have a higher medium-term survival rate after diagnosis, their death rate remains greater than the whole population's, particularly in younger patients. [1]. There is no cure for SLE, however it can be effectively managed with medications. Over the course of 46 years, a population-based study of SLE in the United States revealed an overall decrease in age-standardized mortality of 24.4%, which may have been brought about by advancements in therapy and earlier diagnosis. [2]. Although SLE is considered the classic example of an autoimmune disease, it remains relatively poorly understood. Treatment with immunosuppressive drugs is extremely challenging because of the relative lack of specificity of many of them. Patients treated with maintenance doses of immunomodulatory or immunosuppressive drugs [3]. Currently, the typical medications used in the treatment of SLE are hydroxychloroquine, glucocorticoids, and a variety of immunosuppressive agents [4]. Organ-specific treatments include the use of steroidal and nonsteroidal anti-inflammatory medications, immunosuppressants, and biologics; other considerations include sun protection, diet and nutrition, quitting smoking, exercise, and adequate immunization [5]. For immunosuppressants, scientists have

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found that artemisinin derivatives possess immunosuppressive properties. These kind of antimalaria drugs shows a good efficacy in the adjuvant therapy of SLE. Although these experiments are only in small-scale experiments and is not widely used in the clinic, it can be a expectable drugs curing SLE in the future. This paper introduces the derivatives of artemisinin, dihydroartemisinin and SM934 which show the ability of immunosuppression in animal and clinical trials that might be a more effective and low toxicity treatment as the immunosuppressants. In addition, the comparation between these derivatives and other existing drugs is presented. Therefore, the study aims to evaluate the potential of artemisinin derivatives in immunosuppression by comparing them with existing drugs, hence providing a rationale for their efficacy and safety in clinical applications.

2. Pathophysiology of Systemic Lupus Erythematosus and Pharmacological Properties of Artemisinin

2.1. Pathophysiology of Systemic Lupus Erythematosus (SLE)

Autoimmune disease affecting several systems, SLE is defined by an unusual build-up of T cells that are reactive to oneself and the generation of antibodies against self-antigens. SLE can present with fever, sensitivity to light, rash, enlarged lymph nodes, muscle and joint pain, headache, and fatigue [6]. As with many other autoimmune diseases, the etiology or underlying pathophysiological mechanisms that cause the autoimmune response in SLE remain largely unknown. Several studies have attempted to hypothesise the cause of SLE and to elucidate all possible genetic susceptibility and immunological mechanisms in the pathophysiology of SLE. Over the past 20 years, several studies have shown that genetic susceptibility of SLE is existing [5]. Some said that the pathogenesis of which is mainly the production of pathogenic antibodies by B cells through the aberrant activation of follicular helper T cells (Tfh), thus requiring more effective and safer therapies [7].

2.2. Pharmacological Properties of Artemisinin

Artemisinin was derived from Artemisia annua L., a kind of herb with a long history in China. There is a record in the *Compendium of Materia Medica* about Artemisia annua treating malaria cold and fever, from which Ms. Tu Youyou was inspired to find an effective alternative to chloroquine and a treatment for malaria [8]. The anti-malarial mechanism of artemisinin mainly includes three aspects: Firstly, it exerts an antimalarial effect by generating free radicals. Secondly, it directly kills Plasmodium vivax in the asexual reproduction stage of Plasmodium vivax in erythrocytes. Thirdly, it inhibits the activity of PfATP6 enzyme [9]. From a pharmacological perspective, First, the malaria parasite's body uses iron to catalyze the activation of artemisinin, which cleaves the peroxide bridge in its structure and releases free radicals. Next, the parasite protein undergoes alkylation, a process where the free radicals from the activation step combine with the protein to form covalent bonds that cause the protein to lose its function and eventually die. [10].

In addition, Artemisinin and its derivatives are shown to possess anti-inflammatory activity. The following are some of the anti-inflammatory mechanisms of action: blocking the iNOS and COX-2 pathways; blocking ERK and NF-B signaling; blocking the activation of pathogenic T cells; blocking B-cell activation and antibody production; and blocking Akt phosphorylation and I B degradation via the PI3K/Akt signaling pathway following TNF-. Therefore, it is important to research the potential of phytochemicals produced from Artemisia annua as medication options for the treatment of inflammatory and autoimmune disorders since they have anti-inflammatory actions through a variety of pathways.[11].

3. Derivatives of Artemisinin in Systemic Lupus Erythematosus

3.1. Effect of the Derivatives of Artemisinin on the Pathology of SLE

Its pathogenesis is mainly due to the abnormal activation of B cells through follicular helper T cells (Tfh) to produce pathogenic antibodies In vitro experiments have confirmed that DHA can inhibit the induction of Tfh cells, weakening their helper function in B cell differentiation; in vitro experiments

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have confirmed that DHA can inhibit the induction of Tfh cells, weakening their helper function in B cell differentiation; moreover, DHA has the ability to dramatically lessen the signs and symptoms of lupus nephritis, systemic immunoglobulin (Ig)G, IgM, IgA, and anti-dsDNA in the serum. DHA additionally considerably decreased serum levels of anti-dsDNA, immunoglobulin (Ig)G, IgM, and IgA, as well as the symptoms of lupus nephritis and SLE. To sum up, the findings indicate that DHA directly inhibits B cells by disrupting BTK signaling, and it also inhibits Tfh cells via preventing ITK signaling. Thus, lowering the generation of harmful antibodies may prove to be a successful SLE treatment.[7].

The low solubility of artemisinin and its derivatives has been a barrier to their clinical application. Nevertheless, a water-soluble derivative, β-aminoarteether maleate, SM934, was discovered, which showed 35-fold higher efficacy than dihydroartemisinin in immunosuppressive and cytotoxicity screening tests [12]. The study investigated the therapeutic efficacy of SM934 and its intrinsic mechanisms in lupus-susceptible female NZBNZW F (1) mice. In vivo, treatment with SM934 for 3 or 6 months significantly delayed the progression of glomerulonephritis and improved the survival of NZB/W F (1) mice. The results suggest that the artemisinin analogue SM934 has a therapeutic effect on lupus erythematosus-susceptible female NZB/W F (1) mice by inhibiting the development of pathogenic helper T cells and enhancing the production of the anti-inflammatory cytokine IL-10 [8]. This suggests that SM934 is a potential drug for the treatment of immune-related diseases and can also be effective in the treatment of SLE. Another experiment showed that artemisinin analog SM934 has a therapeutic effect on lupus-susceptible female NZB/W F(1) mice by inhibiting the development of pathogenic helper T cells and promoting the production of the anti-inflammatory cytokine IL-10 [13].

3.2. Safety and Side Effects of SM934

The results of pharmacokinetic experiments conducted on healthy individuals revealed that SM934 was rapidly absorbed, with peak plasma concentrations occurring 0.5–1 hour after oral administration. Additionally, the area under the curve (AUC) for the entire drug exposure was proportionate to the dose between 5 and 60 mg daily. In addition, the oral bioavailability of SM934 in rats and dogs was 11%-14% and 43%-71%, respectively. The elimination half-life of SM934 in rats and dogs was 0.5-1 h. All of these data are the results of preclinical studies and no references are available. Preliminary discovery studies of SM934 showed that it has low cytotoxicity against mouse splenocytes with a CC50 (cytotoxic concentration of a compound that reduces cell viability by 50%) value of 67.3 ± 32.7 μM, while the IC50 (inhibitory concentration of a compound that reduces cell proliferation by 50%) values for its antiproliferative activity were 1.2 ± 0.5 μM and 2.6 μM [12]. The cytotoxicity of SM934 was measured using the MTT assay; the results showed that the toxicity of SM934 was low relative to its antiproliferative activity, with a CC50 (compound toxicity concentration that reduces cell viability by 50%) value of 67.3 ± 32.7 μM. These results suggest that SM934 has a significant inhibitory effect on splenocyte cell proliferation and that the activity observed here is not caused by compound toxicity. The IC50 (compound inhibitory concentration that reduces cell proliferation by 50%) values of 1.2 ± 0.5 μM and 2.6 ± 1.4 μM, respectively.[14].

Table 1. Summary of Cytotoxicity and Suppressive Activities

	Cytotoxicity (CC50, μM)	Proliferation response (IC50, μM)	
	MTT	Con A	LPS
SM934	67.3 ± 32.7	1.2 ± 0.5	2.6 ± 1.4

3.3. Comparison with Existing Treatment Options

Belimumab is the only medication that has been authorized for treatment in SLE in the previous 60 years. The severe side effects of previous medications like cyclophosphamide and glucocorticoids have been somewhat mitigated by newer medications like mycophenolate mofetil and glucocorticoid-free regimens, and ten-year death rates have improved. However, the negative consequences of renal and neuropsychiatric involvement, as well as delayed diagnosis, have impeded further progress. In addition, SLE patients are at increased risk of premature cardiovascular disease and immunosuppressive therapy

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increases the risk of infection. Symptoms such as drug-resistant disease and fatigue remain a problem [15]. As for SM934, it has already mentioned that the tolerant is good and is safe for people. Table 2 shows the side effects of other therapeutic options for SLE. The side effects are often the headache, nausea, vomiting [5]. Comparing with them, dihydroartemisinin shows similar side effect as hydroxychloroquine as both antimalarials, while SM934 shows a less and slight side effects which may be an effective healing efficacy drug in the future.

Table 2. Therapeutic Options reported in the Literature for SLE

Category	Drug	Adult Dosage	Potential Side Effects
Corticosteroids	Prednisone	1–2mg/kg/d	The adverse effects of the drug in question include hyperglycaemia, Cushingoid condition, aseptic necrosis, peptic ulcer, osteoporosis, ecchymosis, glaucoma, cataracts, headache, disorientation, vertigo, adrenal/growth suppression and impaired wound healing.
Antimalarials	Hydroxychloroquine	400–800mg/d	The adverse effects of the medication include aplastic anaemia, leukopenia, thrombocytopenia, corneal alterations or deposits, retinal damage from prolonged use, alopecia, pruritus, changes in skin and musculoskeletal pigmentation, headache, nausea, vomiting, dizziness, irritability, and muscle weakness.
Immunosuppressive agents	Azathioprine	2mg/kg/d	The adverse effects observed in this study included leukopenia (20%), infections, alopecia, fever, diarrhea, hepatotoxicity, nausea, and vomiting. Additionally, thrombocytopenia, Sweet syndrome, and rash were noted.
	Mycophenolicacid	1000-3000mg/d	The adverse effects of the pharmaceutical agent in question include hypertension, tachyarrhythmia, anaemia, leukopenia, blurred vision, constipation, nausea, vomiting, diarrhoea, dyspnoea, haematuria, acne, arthralgia, back pain, colitis, dizziness, fever, gingival hyperplasia, insomnia, cutaneous eruption, and pharyngitis.
	Methotrexate	7.5-15mg/wk	Demyelinating encephalopathy has been associated with a number of factors, including systemic chemotherapy or cranial irradiation, hyperuricemia, salivary gland mucositis, anorexia, intestinal perforation, leukopenia, thrombocytopenia, renal failure, nephropathy, and pharyngitis.

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Table 2. (continued).

	Cyclophosphamide	1–5mg/kg/d	The following symptoms have been observed: haemorrhagic colitis, haemorrhagic cystitis, bladder fibrosis, interstitial pulmonary fibrosis, amenorrhoea, leukopenia, nausea, headaches and hair loss.
	Cyclosporine	2.5–5mg/kg/d	Hyperlipidemia, paresthesia, headache, tremor, hypertension, gingival hyperplasia, hepatic failure, hypertricosis, cramping in the muscles, myalgia, renal failure, and exhaustion
	Tacrolimus	0.06–0.2mg/kg/d	The adverse effects observed included headache, insomnia, nausea, vomiting, constipation, tremor, diarrhea, asthenia, hypophosphatemia, hypomagnesemia, hyperglycemia, and paresthesia.
	Sirolimus (rapamycin)	2–4mg/d	A number of adverse effects have been observed, including hypertriglyceridemia, hypercholesterolemia, arthralgia, constipation, lymphedema, exfoliative dermatitis, neurotoxicity, and hepatotoxicity.

4. Challenges and Future Prospects

4.1. Limitations

As for dihydroartemisinin, firstly, although it showed that DHA blocked ITK and BTK signal respectively to inhibit Tfh and B cells, we do not know the exact proteins and binding sites that help DHA attach to Tfh and B cells. Thus, the further experiment is needed to detect. Secondly, all of the experiments are confined in murine model.so that the clinical trials are needed in the future to examine the efficacy of DHA, optimal usage, and dosing for SLE prevention and management [12]. SM934 had been proved being a low toxicity and high efficacy immunosuppressive agent and shows therapeutic benefits in autoimmune diseases, especially for SLE, which we are talking about throughout the essay. The limitation of today's study is nearly same with dihydroartemisinin, which means that the current experiments are mostly concentrated on animal trials. The good news is that it also conducted the clinical trials on Phase 1 and showed a positive result [13]. However, this is just the beginning of the clinical trial and need longer time to conduct test.

4.2. Directions and Recommendations for Future Research

For both DHA and SM934, they are It has been preliminarily proven to have the effect of immunosuppressants, which might be a useful drug curing SLE in the future. The direction of the two derivatives of artemisinin are obvious. It is that although the results are positive, we have to continue getting more clinical experiments among wider range of people with different age, races, living environments and so on to consolidate and analyze results. Carry out the next phase clinical trials, and the rest problem is just about time, which means we have to be patient and waiting for the lengthy clinical trials. As for the first limitation of DHA, the upstream of ITK and BTK signals in Tfh and B

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cells are TCR and BCR respectively so that DHA may act through TCR and BCR on Tfh and B cells. However, this hypothesis needed to be proved in the future experiments.

5. Conclusion

This paper investigates the pathophysiology of SLE, which may be related to genetic susceptibility and immunological mechanisms, and identifies current therapeutic approaches such as belimumab, nonsteroidal anti-inflammatory drugs, glucocorticoids (for acute or fulminant cases), and some immunosuppressants-SM934. Given the high prevalence and mortality rates associated with SLE among African American and other minority women, the development of highly effective therapeutic agents for the treatment of SLE is of paramount importance. The paper shows two kinds of derivatives of artemisinin- DHA and SM934, acting as immunosuppressant to help with the treatment of systemic lupus erythematosus. In simple words. SM934 reduces Th1 and Th17 cell responses, increases IL-10 secretion, and prevents TLR-triggered B cell activation and PC formation. SLE is caused by increasing the Nrf2 signaling pathway and suppressing the mTOR signaling pathway. Currently, the experiments for DHA are still staying in using mice agent and in phase 1 clinical trial of research of SM934. Future studies should focus on assessing the efficacy and safety of artemisinin derivatives in different populations and delving into their mechanisms of action. Further work also needs to explore how these new drugs can be combined with existing treatment regimens to improve the overall outcome of SLE.

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