Sci. Bull. (2016) 61(1):37–41
DOI 10.1007/s11434-015-0975-9

www.scibull.com
www.springer.com/scp

Review

Life & Medical Sciences

Development of artemisinin drugs in the treatment of autoimmune diseases

Yanwei Wu · Wei Tang · Jianping Zuo

Received: 4 November 2015 / Revised: 3 December 2015 / Accepted: 4 December 2015 / Published online: 26 December 2015

Abstract Artemisinin drugs are a family of sesquiterpene trioxane lactone agents originally derived from *Artemisia annua* L. Due to the big victory in the antimalarial battle, the 2015 Nobel Prize goes to the discoverer of artemisinin-based therapy for malaria. Beyond antimalaria, artemisinin and its derivatives are also being investigated in diseases like schistosomiasis, viral infection, cancers and inflammation. Over the past decades, the anti-inflammatory and immunomodulatory effects of artemisinin drugs have been comprehensively studied. In this article, we will briefly describe the development of artemisinin drugs, especially novel artemisinin derivatives, in the treatment of autoimmune diseases.

Keywords Artemisinin · Autoimmune disease · Anti-inflammatory · Immunosuppressive · SM934

1 Introduction

Since 1971, when a low-temperature ethyl ether extraction of qing hao (Chinese medicinal herb) proved to have antimalarial activity, Chinese scientists have chronicled the discovery and evaluation of a series of antimalarial drugs [1]. Among these, artemisinin, the antimalarial principle of qing hao, was isolated in 1972 [2]. Soon afterward, the derivatives of artemisinin including dihydroartemisinin (DHA), artesunate (ART) and artemether were synthesized and identified for malarial therapy. With the established record of safety in millions of malarial patients, artemisinin and its derivatives are being investigated in diseases beyond malaria, ranging from schistosomiasis, viral infection and cancers to autoimmune diseases [3]. In this article, we will briefly introduce the research progress of artemisinin drugs in the treatment of autoimmune diseases.

The immunosuppressive effects of artemisinin family were first described in 1984, as ART showed inhibition of the proliferation of mitogen-stimulated mouse spleen cells and human peripheral lymphocytes, as well as the spontaneous proliferation of mouse thymocytes and blood cells from some leukemia patients [4]. Subsequently, artemisinin, DHA and arteether were reported to exhibit appreciable suppression of humoral responses in mice, as measured by the hemolytic plaque assay [5]. Despite the discovery of potential immunosuppressive activities in these reports, several shortcomings of traditional artemisinin derivatives including poor solubility and low bioavailability have limited their further application to treat autoimmune diseases.

2 Immunosuppressive activity of artemisinin drugs

There are continuous efforts and increasing interest in developing novel artemisinin derivatives with higher efficacy and better solubility as immunosuppressive agents. The scientists from Zuo's group in Shanghai Institute of Materia Medica (SIMM) synthesized and screened a large number of new artemisinin analogs since 2001, and a series of papers exploring the drug structure–activity relationship

SPECIAL TOPIC: Advances in Artemisinin Study

Y. Wu · W. Tang (✉) · J. Zuo (✉)
Laboratory of Immunopharmacology, State Key Laboratory of Drug Research, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, 555 Zuchongzhi Road, Shanghai 201203, China
e-mail: tangwei@simm.ac.cn

J. Zuo
e-mail: jpzuo@simm.ac.cn

were published [6–8]. Compounds with various modified structures were tested mainly in regard to their cytotoxicity to mice lymphocytes, inhibition activity on ConA-induced T cell proliferation and LPS-induced B cell proliferation, in comparison with artemether, DHA and ART (Table 1). At last, SM735, SM905 and SM934 (Fig. 1), which showed both great solubility and wide therapeutic window, were selected for further evaluation of in vitro and in vivo immunosuppressive activities.

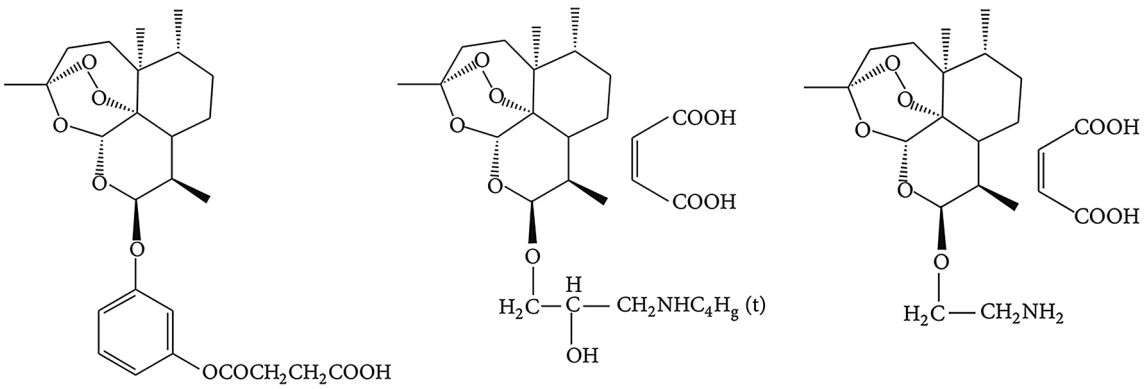
In case of autoimmune disorders, stubbornly ongoing inflammation is the primary aspect. This, particularly, is accompanied by specific humoral and cellular immune responses that are orchestrated by pro-inflammatory mediators. In the studies, SM735, an oil-soluble artemisinin derivative, was found to exert an inhibitory action on pro-inflammatory cytokine production including IL-12, IFN-γ and IL-6 in mice splenocytes by mitogen stimulation [10]. With wonderful water solubility, SM905 and SM934 also exhibited potent anti-inflammatory and immunosuppressive effects on mice splenocytes with mitogen stimulation [11, 12]. Besides, SM905 inhibited NO and pro-inflammatory cytokine production by suppressing MAPK and NF-κB pathways in RAW 264.7 macrophages [13]. Later in animal experiments, SM735 strongly suppressed both T cell-mediated delayed-type hypersensitivity (DTH) reactions and B cell-mediated quantitative hemolysis of SRBC (QHS) reactions [10]. As for SM934, it not only inhibited SRBC-induced DTH response, but also suppressed antigen-specific T cell activation on OVA-immunized mice model [12]. By that time, the immunosuppressive activity of those new compounds was basically explicit.

3 Artemisinin drugs in experimental autoimmune encephalomyelitis (EAE)

From the year of 2001, Zuo's group devoted to proving the immunosuppressive functions of the novel artemisinin derivatives including SM735, SM905 and SM934 in vitro and in vivo. In the meantime, Zang et al. studied on the immunosuppressive properties of SM933, another artemisinin derivative discovered by Zuo's group. They reported that SM933 possessed unique anti-inflammatory properties through regulatory mechanisms involving the NF-κB and the Rig-G/JAB1 signaling pathways, leading to amelioration of experimental autoimmune encephalomyelitis (EAE) [14]. EAE is a well-established murine model of human multiple sclerosis (MS), an autoimmune disease occurring

Table 1 Immunosuppressive activity of artemisinin drugs

Compounds	IC_{50} (μmol/L)			CC_{50} (μmol/L)	References
	ConA	LPS	Alloantigen		
Artemether	6.3 ± 1.9	2.4 ± 1.5	3.5 ± 0.6	80 ± 0.4	[9]
DHA	6.0 ± 1.5	1.2 ± 0.3	0.82 ± 0.45	9.4 ± 1.0	–
ART	2.4 ± 0.6	0.6 ± 0.1	0.83 ± 0.48	6.8 ± 2.5	–
SM735	0.33 ± 0.06	0.27 ± 0.02	0.86 ± 0.18	53.1 ± 7.8	[10]
SM905	1.33 ± 0.37	0.31 ± 0.08	0.67 ± 0.12	79.6 ± 6.0	[11]
SM934	1.2 ± 0.5	2.6 ± 1.4	2.11 ± 0.76	67.3 ± 32.7	[12]



SM735 SM905 SM934

Fig. 1 Chemical structure of novel artemisinin derivatives