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Review Article

Artemisinin resistance: an important emerging clinical problem in tropical medicine

Sora Yasri[1], Viroj Wiwanitkit[2,3]

[1]*KMT Primary Care Center, Bangkok, Thailand;* [2]*Hainan Medical University, China;* [3]*Dr DY Patil University, India*

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Abstract: Artemisinin is an important antimalarial drug which is originated and developed from Chinese traditional herbal regimen. At present, artemisinin is used as an antimalarial drug for treatment of drug resistant malarial infection. The effectiveness of artemisinin is clinically accepted. Hence, artemisinin is currently used as main drug for malaria treatment in many tropical countries. Artemisinin resistance is a new emerging clinical problem in tropical medicine. New mutation can result in artemisinin resistance and the resistance becomes important new emerging problem in clinical malariology. It is necessary to control of artemisinin use and searching for new effective drug against artemisinin resistant malaria. In this article, the authors summarizes on important updated information regarding artemisinin resistance.

Keywords: Artemisinin, resistant, malaria

Introduction

In tropical medicine, mosquito borne infectious disease is an important group of medical disorders. In tropical medicine, there are many kinds of mosquito borne infections. Malaria is an important blood parasitic infection caused by *Plasmodium spp*. At least five species of Plasmodium parasite cause malaria. At present, malaria affects millions of world population living in tropical endemic countries. Annually, a high incidence of malaria is reported from many tropical zones of the world, such as Africa, Indochina and South America. Hence, malaria is still a global public health problem.

Clinically, malaria is an acute febrile illness. The mosquito vector is *Anopheles spp*. After being bitten by mosquito vector, an infection in red blood cell can occur and causes clinical problems. A patient usually has a high fever with chills. Hemolysis can occur and can result in a severe clinical manifestation. Systematic complications include renal problems and cerebral involvement. In a severe case, the patient might die.

For malaria therapy, the antimalarial drug is indicated. Antimalarial drugs have been discovered for decades. Examples of classical drugs are quinine and primaquine. The efficacy of the antimalarial drug is a main determinant for success in malaria therapy [1]. At present, the classical antimalarial drugs are considered not effective in malaria therapy because of antimalarial drug resistance problem [1-3]. Hence, new antimalarial drugs, such as artemisinin, are used for malaria therapy in endemic countries instead of classical drugs.

Artemisinin is an antimalarial drug developed from a Chinese traditional herb, Qinghao. At present, artemisinin is presently indicated for treatment of malaria that is resistant to the classical antimalarial drug, quinine [4]. The high effectiveness of artemisinin is reported; hence, it is currently used in many tropical endemic countries where quine resistance is common. However, a new emerging problem, artemisinin resistance, has already occurred. The artemisinin resistance is a new problem in tropical medicine that requires an urgent management. Many endemic countries found the new mutations leading to the artemisinin resistance. Hence, Artemisinin resistant malaria becomes a new clinical problem in tropical medicine. Artemisinin use without indication must be controlled. Also, it is necessary to search for new

antimalarial drugs against Artemisinin resistant malaria.

Since artemisinin resistance is a new problem and there are few data on this problem for clinical practitioners, the aim of the present article is to summarize important updated clinical information regarding Artemisinin resistance.

Epidemiology of artemisinin resistant malaria

The artemisinin-resistant malaria is a new emerging problem in clinical malariology. Artemisinin resistance currently occurs in many tropical countries. Artemisinin resistance was firstly reported in tropical Asia, where the malaria is highly endemic. This is similar to the previous first observation on classical antimalarial drug resistance, which was firstly reported from tropical Southeast Asia. Sinha et al. noted that artemisinin use could reduce the mortality rate of malaria worldwide, but the emerging artemisinin resistance problem in Cambodia-Thailand border might be the big problem significantly decreased usefulness of artemisinin [5]. The poor control of rational antimalarial drug use in tropical Asia is an important factor inducing the antimalarial drug resistance.

At present, Indochina countries are the main area with many reports on new emerging Artemisinin resistance. The international border areas in Southeast Asia, especially Thailand-Cambodia border and Myanmar-China border, are the main affected areas of artemisinin resistance [5, 6]. Ye et al. mentioned for the importance of underlying genetic factor that resistant parasites usually carried distinct halplotypes reflecting the multiple indigenous origins of the resistant alleles [6]. Ye et al. recommended for surveillance of resistance in all malaria endemic areas where artemisinin was generally used [6]. Regarding the other tropical regions of the world, such as tropical Africa, there is still no problem of artemisinin drug resistance [7]. However, it is necessary to closely monitor the changing situation. Since multidrug resistant malaria is an important public health problem at present and already observed in several non-tropical countries, such as Italy [8]. The new emerging artemisinin resistance might superimpose the global antimalarial drug resistant situation.

Contributing factors for artemisinin resistance

The present emerging artemisinin resistance occurs at Indochina, the same region as the quinine resistance previously originated. The main factor that might lead to the problem is the non-rational antimalarial drug use. Poor quality control in antimalarial drug production and uncontrolled antimalarial drug sale and distribution are basic problems in this area [9, 10]. Pongtavornpinyo et al. noted that antimalarial drug resistance is caused by incorrect use of antimalarial drug [11]. Pongtavornpinyo et al. noted that use of the drug at an inappropriate dosage can induce resistance of parasites [11]. At a low drug level, parasite might develop tolerance and can achieve a survival advantage [11]. In Cambodia, the antimalarial drug including to artemisinin can be easily available and self-administered without prescription [12]. Hence, use of antimalarial drug without confirming diagnosis is common and considered irrational. Littrell et al. also noted for the widespread use of antimalarial drug cocktails which might result in poor malaria control [12].

Pathogenesis of artemisinin resistance

The antimalarial drug resistance is related to the genetic background. The main cause of artemisinin resistance is the mutation of the parasite. When a sense mutation occurs, the resistance to antimalarial drug develops. There are many studies reported on genetic factor causing resistance. Focusing on artemisinin resistance, many genetic polymorphisms are studied for the clinical association with drug susceptibility to artemisinin. Important genetic polymorphisms which are mentioned for clinical association with artemisinin resistance are hereby discussed.

Polymorphisms of K13

Polymorphisms of K13 are proposed for clinical association with artemisinin resistance (**Table 1**) [8, 14-18]. Ménard et al. noted that mutations in portions of a Plasmodium falciparum gene encoding kelch (K13)-propeller domains were the major determinant of resistance and noted that it might further progress to on a global scale resistance problem [13]. Ménard et al. recently reported the “worldwide map of *P. falciparum* K13-propeller polymorphisms”

Table 1. Important reports on polymorphisms of K13 and artemisinin resistance

authors	Details
Conrad et al. (2014) [8]	Conrad et al. reported the association between polymorphisms in K13 and artemisininin resistance in Ugandan children [8]. Conrad et al. (2014) found that mutant was not prevalent in isolated *P. falciparum* samples.
Nyunt et al. (2017) [14]	Nyunt et al. reported that mutated type K13 was common in Myanmar [14]. Nyunt et al. mentioned for the clinical association between the genetic underlying factors, including polymorphisms in k13 gene, and the incidence of artemisinin resistance in Myanmar [14].
Torrentino-Madamet et al. (2014) [15]	Torrentino-Madamet et al. reported on limited polymorphisms in k13 gene in malarial pathogen isolates from Senegal [15].
Tacoli et al. (2016) [16]	Tacoli et al. found that specific K13 mutations (P574L and A675V, contributed to resistance [16]. Tacoli et al. noted that those mutants were common in southeast Asia where artemisinin resistance is an emerging problem [16].
Mayengue et al. (2018) [17]	Mayengue et al. reported on no K13 polymorphism related tp artemisinin resistance in Congo [17].
Madamet et al. (2017) [18]	Madamet et al. reported on no K13 polymorphism related tp artemisinin resistance in Senegal [18].

and concluded that Artemisinin resistance was confined in Southeast Asia and China, which was concordant to a locally confined resistance-associated K13 mutations in this area [13]. Ménard et al. also mentioned that most African mutations were neutral and common African A578S allele was not related to in vitro or clinical resistance to artemisinin [13]. According to updated data on molecular epidemiology of polymorphisms of K13 in parasite isolates circulating in other region of the world, low frequencies of resistance-associated K13 mutations are observed in South Asia [19]. Another report from Northern Uganda also showed an independent emergence and local spread of clinically artemisinin-resistant parasites during 2017 through 2019 [20]. Similar report from Equatorial Guinea also highlights the emergence of artemisinin outside Indochina [21]. Based on the data from those new areas, a good surveillance for early detection of possible emerging problem in the new area is needed [19].

Polymorphisms of falcipain-2

Falcipain-2 polymorphism is another genetic polymorphism that might have an association with artemisinin resistance. Conrad et al. (2014) found no association between falcipain-2 polymorphisms and artemisinin resistance [8]. Conrad et al. also observed that the mutant was not prevalent in falciparum parasite isolated from Ugandan pediatric patients [8]. However, Siddiqui et al. recently studied on alciparum falcipain-2a polymorphisms in Southeast Asia and clinical association with artemisinin resistance and found that altered hemoglobin digestion due to FP2a mutations could lead to artemisinin resistance [22].

Management of artemisinin resistant malaria

Generally, antimalarial drug resistance usually results in a requirement for an increased dosage or combination of many antimalarial drugs or new more effective antimalarial drug [23]. Considering artemisinin resistance, slow parasite clearance among malaria-infected patients is the main problem [24]. This resistance is due to single nucleotide polymorphisms can result in reduced efficacy of artemisinin [24]. Hence, it is necessary to prevent the development of drug resistance. Pongtavornpinyo et al. noted that mosquito vector control, limiting presumptive antimalarial drug use and avoidance of combination therapies containing drugs with mismatched half-lives were key points for limiting spreading of artemisinin resistance [11]. Fairhurst and Dondorp noted that it was necessary to monitor drug efficacy where K13 mutations are prevalent [25]. Fairhurst and Dondorp also noted that searching for new effective antimalarial drug was necessary [25]. The tetraoxane, a synthetic endoperoxide-based antimalarial drug candidate, is the new interesting

substance proposed for management of artemisinin resistant malaria [26]. Oliveira et al. noted that "*hybrid compounds, comprising endoperoxides and vinyl sulfones, were capable of high activity profiles comparable to Artemisinin and chloroquine while acting through two distinct mechanisms of action: oxidative stress and falcipain inhibition*" [27].

Perspective on artemisinin resistance

Artemisinin resistance might expand from its original site in Indochina to many areas around the world. Although artemisinin resistance does not currently distribute to South Asia and South America [28], there is a chance. The similar phenomenon to that observed in quinine resistance might occur. It is necessary to have an international collaboration of surveillance system. Based on authors' view, it is urgently need that local public health policy makers have to set a plan to correspond emerging problem. A strict control of artemisinin use is required. Irrational use of artemisinin without indication must be controlled. Additionally, a strict control of drug distribution without the official diagnosis of malaria and physician's prescription has to be set. For the management of artemisinin resistance in endemic areas, synthetic endoperoxide antimalarial is the new hope and requires further clinical researching on its effectiveness [29].

Conclusion

Artemisinin resistance is an important new emerging problem in tropical medicine. The poorly controlled antimalarial artemisinin use without indication is the main contributing factor for drug resistance. The problem currently occurs in tropical Asia, where inappropriate use of artemisinin is common. For a few years, an emerging problem has just been recently reported from Africa. Genetic mutation inducing artemisinin resistance is reported as an underlying genetic factor. The artemisinin resistance is expected to be a new public health problem if there is no urgent management. The control of non-rational antimalarial drug use is necessary for limiting the expansion of the problem. Also, searching for new more effective antimalarial drugs to combat the emerging artemisinin resistance should be set as high priority research in clinical malariology.

Disclosure of conflict of interest

None.

Address correspondence to: Sora Yasri, KMT Primary Care Center, Bangkok, Thailand. Tel: +66-262626222; E-mail: sorayasri@outlook.co.th

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