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SHORT COMMUNICATION:

A Clinical approach to the treatment of Artemisinin-Resistant *Plasmodium falciparum* Malaria in India

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ABSTRACT

Treatment failure in P. *falciparum* Malaria is a major dilemma that faces health care workers throughout the country. True Artemisinin-resistance is one of the causes after ruling out compliance and drug quality issues and Sulphadoxine-Pyrimethamine resistance. The other cause is re-infection with a new strain of the parasite during the treatment period.

It is found that a combination of oral Quinine and oral Clindamycin can be given for Artemisinin-resistant *P. falciparum* Malaria patients living in the North-East of India. Those living in the rest of the country should first be treated for Sulphadoxine-Pyrimethamine resistance with Artemether-Lumefantrine. If there is no response, they can be given Quinine and Clindamycin.

Awareness among health care providers on how to treat Artemisinin-resistant *P. falciparum* Malaria can be improved. This paper addresses this issue.

Keywords: Malaria, Drug resistance, *Plasmodium falciparum*, Quinine, Clindamycin

Introduction

Artemisinin resistance occurs due to *Kelch 13* gene single nucleotide polymorphisms of *Plasmodium falciparum.* As a result, the pro-oxidant action of artemisinins is antagonized. [1]

In a study done in West Bengal state of India from April 2014 to January 2016, out of fifteen patients, thirteen patients had *pfkelch13* G625R polymorphism, whereas two patients had R539T polymorphism. Using the W.H.O. criteria, these fifteen isolates would be considered artemisinin-resistant isolates.[2]

In a study done in the Pune district in India, although the markers associated with artemisinin resistance such as mutations in *pfkelch13* and R539T were not detected, however, mutations in both *pfdhfr* and *pfdhps* were both prevalent and indicated Sulphadoxine-Pyrimethamine resistance.[3]

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The therapy of Malaria due to *P. falciparum* in India is dependent on the patient's residence. If the patient resides in any part of the country except the eight North-Eastern states, he/she is treated with an Artemisinin Combination Therapy (ACT) consisting of 3 days treatment with Artesunate and 1-day treatment with Sulphadoxine-Pyrimethamine along with 1-day treatment with Primaquine. The role of Primaquine is to kill the gametocytes. If a patient resides in any of the eight North-Eastern states, he/she is treated with a combination of Artemether and Lumefantrine for 3 days because drug resistance to Sulphadoxine-Pyrimethamine had been observed in these eight North-Eastern states and so Lumefantrine was chosen to replace Sulphadoxine-Pyrimethamine in these areas.[4]

A dilemma that faces the health worker is what should be done if a patient, despite full compliance with treatment and no history of vomiting or diarrhea, does not respond parasitologically. If it is a case of *P. falciparum* Malaria, this treatment failure could be either due to true drug resistance or due to re-infection by a new strain of *P. falciparum* within the treatment period. [5]

It is difficult for the health care provider to differentiate between the above two possibilities in the field. This paper aims to provide a practical solution as to what he/she can do when faced with such a dilemma.

Material and Methods

The study design included analysis of the documents of the NCVBDC about the treatment of drug-resistant *P. falciparum* Malaria. Also, published literature was obtained on the use of currently recommended drugs being used for the therapy of Malaria resistance to Artemisinins.

Results

According to the operational document on Malaria Elimination in India published in 2016, resistance is suspected if, despite complete treatment and absence of vomiting or diarrhea, the patient does not respond clinically and parasitologically within 3 days. In such cases, it is advised to give Quinine with Tetracycline, Doxycycline, or Clindamycin. [6]

The role of Quinine with Doxycycline or Clindamycin as an alternative to Artemisinin in the treatment of *P. falciparum* Malaria is also mentioned by Koehne et. al.[7]

Discussion

A problem that would arise is if the patient is a child because Tetracycline and Doxycycline are contraindicated in this age group. However, Clindamycin is suitable for children. In that case, the following regimen may be used for Artemisinin-resistant *P. falciparum* Malaria in both children and adults:

1. Tab Quinine 15 mg per kilogram body weight BD for 3 days [7]
2. Cap or Syrup Clindamycin 7 mg per kilogram body weight BD for 3 days [7]

The above regimen may be implemented immediately for patients living in the eight North-East states. However, for those patients living in the rest of the country, before treating for Artemisinin-resistance, it would be better to treat first for partner-drug resistance i.e., resistance to the Sulphadoxine-Pyrimethamine component. This can be done by using the Artemether-Lumefantrine combination as follows:

Artemether-Lumefantrine is to be prescribed as per body weight:

▪ 5 kilograms to 14 kilograms	▪ 20 mg Artemether plus Lumefantrine 120 mg
▪ 15 kilograms to 24 kilograms	▪ 40 mg Artemether plus Lumefantrine 240 mg
▪ 25 kilograms to 34 kilograms	▪ 60 mg Artemether plus Lumefantrine 360 mg
▪ 35 kilograms & above	▪ 80 mg Artemether plus Lumefantrine 480 mg

Artemether-Lumefantrine is not to be given to children weighing less than 5 kilograms.

These are available as Artemether 20 mg plus 120 mg Lumefantrine and 40 mg Artemether plus 240 mg Lumefantrine dispersible tablets for Children. For Adults, Artemether 80 mg plus 480 mg Lumefantrine tablets/capsules are available.

A total of 6 doses to be administered:

• *The first dose at the time of diagnosis*
• *Second dose after a gap of 8 hours*
• *Third dose after 24 hours*
• *Fourth dose after 36 hours*
• *Fifth dose after 48 hours*
• *Sixth dose after 60 hours*

It is important to also give Primaquine at a dose of 0.75 mg/kilogram body weight on Day 2 of therapy to kill gametocytes. Primaquine is not to be given to children less than 1 year of age.

Conclusion

If a patient (child or adult) living in any of the eight states of North-East India develops drug resistance to ACT consisting of Artemether and Lumefantrine, he/she can be given Quinine and Clindamycin at the doses recommended above.

If a patient (whether child or adult) living in any part of India except the eight states of the North-East develops drug resistance to ACT consisting of Artesunate and Sulphadoxine-Pyrimethamine, he/she can first be given Artemether and Lumefantrine to take care of Sulphadoxine-Pyrimethamine resistance. In case there is no response, he/she can then be given Quinine and Clindamycin at the doses recommended above taking care of Artemisinin resistance.

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