LETTER TO THE EDITOR

Ann Ibd. Pg. Med 2020. Vol.18, No.1 85-86

LATE RECRUDESCENCE OF *PLASMODIUM FALCIPARUM* AFTER ARTEMISININ BASED THERAPY SUGGESTS A NEED FOR PROLONGED FOLLOW UP DURATION

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Artemisinin based combination therapies (ACTs) are the corner stone of current efforts aimed at the management and control of malaria globally.[1] In 2004, Nigeria adopted the recommendation of the World Health Organization and made two ACTs (artemether-lumfanthrine and artesunate Amodiaquine) the first line malaria therapies. Several studies have confirmed the high efficacies of these therapies.[2] However, in 2009, resistance to Artemisin was reported from South-east Asia.[3] Since then, fears of resistance to artemisinin in sub-saharan Africa have been entertained. Recent publications from workers in Nigeria are pointing towards a decline in malaria parasite susceptibility to artemisinin-based combination therapies.[4] These reports are worrisome and there is a need for interventions and methods that will delay the development of artemisinin resistance in the sub region. This letter describes an observation that suggests the need for prolonged follow up of malaria patients after treatment with artemisinin-based therapies in order to monitor properly the pattern of recrudescence to ACT therapies. The following report will contribute to background data and the need for prolonging the follow up period in antimalarial studies that may be essential to the monitoring of recent trends to artemisinin-based therapies in Nigeria.

In a study conducted at the University College Hospital, Ibadan, in Southwest Nigeria in 2004, one hundred and ten (110) children aged below 12 years (mean age 5.9 ± 2.9 years with acute uncomplicated malaria received Artesunate-Mefloquine (AMq) and were followed up for 42 days. The study was approved by the Institutional Ethics Review Board and all participants gave written informed consent. The follow-up schedule included blood smears for microscopy and Polymerase Chain Reaction (PCR) for genotyping of parasites on days 1, 2, 3, 7, 14, 21, 28, 35, and 42. Enrolled children had parasitemia of 2000/uL or greater. The children were treated with a standard dose of Artesunate (4mg/kg) and Mefloquine (25mg/kg) combination for three days. Drugs were administered orally. Parasite clearance time in days before parasite cleared from the peripheral blood film was determined. Parasite genomic DNA was extracted from blood samples collected on filter paper using the Chelex extraction method according to the method described by Plowe *et al* 1995.[5] In the study, polymorphism in block 3 of merozoite surface protein 2 (MSP2) in *P. falciparum* isolates was used for parasite genotyping. Analyses of treatment outcome (re-infection vs. recrudescence) was carried out using parasite MSP2 loci that exhibited repeat numbers of polymorphisms to detect the complexity of infection in individual patient isolate as well as distinguish true treatment failure (recrudescence) from new infection (re-infection).

The results showed that the geometric mean parasite density was 85,089 parasites/μL, parasite clearance time was 1.4 ± 0.5 days and parasite reduction ratio was 75.4 x 10^3 per day for the children studied. During the course of follow-up children remained without patent parasitemia until day 21 at which time nine late treatment failures occurred as shown in the table. Analysis of parasite genotypes showed that five of the late treatment failures were recrudescence, while four were re-infections. There was no occurrence of mixed re-infection and recrudescence in any of the children that failed therapy.

The occurrence of late parasite recrudescence was unexpected at the time the study was carried out. At that time, there was a general tendency to attribute parasite re-infections to late treatment failures and recrudescence to treatment failure before day 14 of antimalarial therapy. At about the same period, studies starts showing that distinguishing re-infection and recrudescence was better done by molecular differentiation and not by attributing late treatment failures to re-infection and early treatment failures to recrudescent parasites.[6] In light of recent decline in susceptibility to ACTs in Nigeria[4] it has become imperative suggest compliance to a follow up period

of 42 days minimum and mandatory molecular differentiation of parasite recrudescence and re-infection in all antimalarial studies. The relevance of longer durations of follow up in the setting of current malaria drug trials have been described in a few studies[7], however studies are still being conducted in the sub-region and globally with follow up periods of 28 days, many times on account of financial implications and participants' inability to completing the study.

Ensuring a follow up period of a minimum of 42 days (the longer the duration of follow up the more advantageous in the case of monitoring for recrudescent parasites) will enable proper documentation of local trends in recrudescence to antimalarial treatment so as to determine appropriate therapies that will rapidly eliminate parasite recrudescence and clear recrudescent parasites from the blood of infected patients. The usual 28 day follow-up period should be discouraged and molecular differentiation between parasite recrudescence and re-infection be made mandatory. The development of rapid point of care immunochromatographic tests to differentiate between malaria parasites recrudescence and re-infection will significantly support interventions aimed at delaying the emergence of artemisinin resistance in Nigeria and the sub-region. Undetected recrudescence in the community will encourage the spread of parasites with decreased susceptibility to artemisinin therapies.

Table: Parasitological characteristics of the nine patients that failed therapy

Patient	Age (Yrs)	Parasite density at enrollment (/uL)	PCT (days)	Day of failure	Parasite density at failure (u/L)	Outcome	PCR correction
012	6.00	4,477	1	27	36	LTF	RECRUD
O35	2.83	61,330	2	35	26,636	LTF	REINF
048	8.00	16,374	1	42	8,041	LTF	REINF
054	6.00	9,877	3	42	58,970	LTF	RECRUD
064	7.00	18,870	2	28	8,067	LTF	RECRUD
073	4.00	42,000	2	35	1,000	LTF	RECRUD
084	11.00	24,000	2	42	120	LTF	REINF
100	9.00	227,272	1	21	13,980	LTF	RECRUD
110	6.00	116,279	1	42	12,005	LTF	REINF

Legend: PCT = parasite clearance time in days, RECRUD = Recrudescence, REINF = Reinfection

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