

Review Article

Recrudescence Malaria

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Abstract

Recurrence of malaria after antimalarial treatment can be due to recrudescence. During recrudescence malaria, the symptoms are lesser compared to primary infection and the gametocytaemia:parasitaemia ratio is higher. A combination of artemisinin derivative drug with one or more long acting antimalarial drug prevents recrudescence.

Plasmodium falciparum malaria recurrences after a complete treatment can occur by two different mechanisms, reinfection or recrudescence.¹ Recrudescence result from persistent erythrocytic infection, which re-emerges within a defined period following antimalarial treatment. This period is dependent mainly on the susceptibility of the infection and the elimination kinetics of the antimalarial treatment.²

Recrudescence can be due to a) incomplete or inadequate treatment as a result of drug resistance or improper choice of medication b) an antigenic variation c) infection by different strains. Following treatment with rapidly eliminated drugs, most recrudescence occur within four weeks, but following treatment with slowly eliminated antimalarial drugs, the recrudescence may be delayed.²

Hence, a recurrence of parasitaemia within 28 days of the antimalarial treatment is often considered as recrudescence infections in most malaria-endemic areas. However, infections recurring between day 14 and 28, post-treatment in areas of high transmission could

be due to newly acquired infections.³ Unexpected high new infection rates have been observed as early as day 7, post-treatment.⁴

In endemic areas it is not possible clinically to distinguish a recrudescence from a newly acquired infection or, in a case of *Plasmodium vivax* infection, a relapse.² In a study where clinical features of the primary *Plasmodium falciparum* infections and of the recrudescence infection that emerged after antimalarial treatment were evaluated, it was found that compared with the primary infections, the recrudescence infections were accompanied by significantly fewer symptoms.⁵ In the peripheral blood evaluation during recrudescence, the gametocytaemia: parasitaemia ratio is found to be higher compared to primary infection.⁵

Polymerase chain reaction for genotyping of malarial parasites with analysis of bands on gel electrophoresis helps to differentiate re-infection from recrudescence.^{4, 2} Detection of genetic diversity in antigenic loci has enabled confirmation of recrudescence infection in paired samples taken from patients prior to and after antimalarial treatment.³

Treatment for uncomplicated falciparum malaria should have high cure rates. The

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World Health Organization has recently set a target cure rate of 95% assessed at 28 days.² Cure is said to have occurred when after the antimalarial treatment, the patient's symptoms resolve, parasitaemia becomes undetectable and there are no recrudescences of infection with the genotype which caused the original illness.²

However, the *in vivo* response of *P. falciparum* to antimalarial drugs is modulated by a number of factors. These include the pharmacokinetic properties of antimalarial drugs, innate and acquired immunity in the patient, as well as the complexity of infections in high transmission areas.³ The *in vivo* clinical efficacy studies of antimalarial drugs include clinical and parasitologic responses, as well as genetic polymorphism analysis to distinguish between recrudescence infection and reinfection.³

Resistance of *Plasmodium falciparum* to antimalarial drugs remains a major problem for treatment of malaria infections in most endemic areas. Tracking the spread of drug resistant malaria is a major challenge for the global control of the disease.³

Deaths due to malaria are occurring in increasing numbers because of frequent failure of the conventional treatments using drugs such as chloroquine and sulphadoxine-pyrimethamine, against which *P. falciparum* populations have developed high degree of resistance.⁶

Artemisinin has a high therapeutic index in the treatment of malaria. It is a compound extracted from the Chinese herb, sweet wormwood *Atemisia annua* plant. It has been used in China in the treatment of fevers for more than 1000 years.⁷ Artemether, arteether, artesunate, artemether and dihydroartemisinin are some of the antimalarials semisynthesized from artemisinin, which are relatively more potent

than artemisinin.⁶

However, in the case of artemisinin based drugs as monotherapies, the recrudescence rate is high and there is the possibility of emergence of artemisinin resistant *P. falciparum* strains.⁷

Artemisinin based combination therapy (ACT) is a scientific approach to tackle this problem. It is a combination of artemisinin derivative drug with one or more long acting antimalarial drug having different modes of action and different drug targets. Artemisinin drugs have a short half-life of 1-4 hours, but because of their strong anti-plasmodial activity, they reduce the biomass of the existing parasites by 95% at each dosage of administration, and also kill the sexual stages of the malarial parasite. Residual parasites, if any, and the recrudescences are eliminated by the long acting antimalarial drug and the host immunity.⁷

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EXENATIDE ONCE WEEKLY IN TYPE 2 DIABETES

Patients with type 2 diabetes who have not achieved adequate glucose control at the maximum tolerated doses of their oral therapies have had no alternative other than insulin. However, the best insulin regimen is a matter of controversy because addition of biphasic, prandial, or basal insulin to oral therapy has been proposed. Besides the fear of subcutaneous injections, the two main objections raised by the patient (and often also by the physician) are the risk of hypoglycaemia and weight gain.

Exenatide is the first of new class of compounds and has similar activity to the naturally occurring hormone glucagon-like peptide 1, improving glycaemic control through glucose-dependent stimulation of insulin secretion, suppression of glucagon secretion, slowing of gastric emptying and reduced appetite. Exenatide 10 µg twice a day might enable patients with type 2 diabetes to improve glycaemic control and reduce or eliminate weight gain and the risk of hypoglycaemia.

Exenatide therapy can be regarded as an alternative to insulin in patients with treatment failure on oral agents.

These investigators showed that long-acting exenatide 2 mg once a week resulted in significantly greater improvements in glycaemic control than did exenatide given twice a day, with no increased risk of hypoglycaemia, lower occurrence of nausea, and similar reductions in bodyweight. Interestingly, such benefits were observed with long-acting exenatide when added to a broad spectrum of glucose-lowering therapies (except insulin).

Indeed, the initial enthusiasm might shift to scepticism when first concerns about effectiveness, safety, or both arise. Many glucose-lowering drugs were withdrawn from the market or their use became controversial despite early positive results.

Exenatide is *not* yet considered in international consensus guidelines. The update NICE guideline recommended to offer exenatide only when insulin would otherwise be started, obesity is a specific problem (body-mass index > 35 kg/m²), and the need for a high dose of insulin is likely. When the once-a-week exenatide formulation becomes available, after confirmation and extension of today's positive results, this new strategy might substantially change the management of type 2 diabetes.

Andre J Scheen, *The Lancet*, 2008; 372 : 1197-98.