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Protection after Malaria Therapy: A Step-up to Immunity

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Abstract

The recognition of deficiencies in control programs of antimalarial vaccines and drugs have acquired importance as a frontline protection in malaria therapy. Since antimalarial drug resistance has been reported for all existing drugs worldwide, leaving combination therapy, this includes artemisinin and its derivatives, as the only choice of chemotherapy. In case of artemisinin combination therapy, it is very interesting to know that once the protection is noticed after the treatment in experimental malaria model, they get protected for second, third and subsequent infections. This is also true in case of infected patients in malaria endemic areas. The picture that emerges is of that immunity to malaria is playing a main role during infection. However, the protection after antimalarial drug treatment also gives us a picture that the protection leads to a step-up in immunity.

Keywords: Malaria; Immunity; Artemisinin; Plasmodium

Background

Malaria, a mosquito-borne disease caused by a protozoan of genus Plasmodium, is the main cause of death in children, pregnant women and immune-depressed people in disease prevalent countries [1]. Most affected are underdeveloped countries with 60% of the deaths caused by the disease [2,3]. Recent estimates show that deaths in children, worldwide, below the age of five have fallen by 47-54% since 2000 [4]. This success is due to the availability of new, improved, safe and highly effective antimalarial drugs. Since 1990, then a potential Chinese herbal drug artemisinin [5] is now a drug of choice for treatment of drug-resistant malaria [6].

Mutations that change the primary amino acid sequences of the specific target genes will be the main cause for drug resistance in global scenario. These will serve as a key molecular marker for identifying resistant parasites. Point mutations with respect to parental drugs chloroquine (pfcrt [7] and mdr1 [8], sulfadoxine-pyrimethamine (dhfr and dhps) [9] have lead to drug resistance. Artemisinin treatment was away from resistance problems but this too has fallen in the basket of drug resistance. Recently, a study on K13-properller mutations in the kelch motif containing gene has been identified for artemisinin resistance [10]. It has shown good response in both *in vitro* [11,12] and *in vivo* [13-16] conditions.

A promising new approach, of the several proposed/implemented, that has gained increasing attention worldwide is the use of combination drugs that are safe, well tolerated and efficacious; and clears all stages of parasite development. In particular, artemisinin combination therapy (ACT) is the preferred choice [17]. ACTs are now a WHO recommended first-line of treatment for malaria [18] and thus play a very important role in global malaria eradication [19]. Currently tested antimalarial artemisinin combination regimens in malaria endemic areas are atesunate + lumefantrine (oral reparations), artesunate (injection for IV and IM), artesunate + mefloquine (oral preparations), artesunate + amodiaquine (oral reparations) and artesunate + sulphadoxine/pyrimethamine (oral preparations).

A concern with several ACT partner drugs are that the malaria parasites have started developing resistance, as they effectively become unprotected monotherapies once artemisinin effect had been compromised [20,21]. Once drug starts clearing the parasite, parasite will find the other way to survive by drug resistance. Artemisinin produce speedy clearance of parasitemia and quick relief by reducing the parasite load, which is higher than the other currently available antimalarials.

Replacement artemisinin derivative-based combinations with partners like amodiaquine [22], sulfadoxine-pyrimethamine [23], mefloquine [24], piperaquine [25] and lumefantrine [26] could not prolong for long term protection. Although efficacious, these combinations have drawbacks as well. Thus, several groups in recent years are working with naturally existing medicinal plants like piperiquine [27], curcumin [28,29] and garlic [30] in ACT group. All are from natural sources of long term use and as such no resistance is known for any partner drugs, and is used as dietary supplement. Many of these artemisinin combinations have shown parasite clearance and complete protection after the drug treatment in rodent model of malaria. Studies in our laboratory for the first time has shown that arteether (a derivative of artemisinin) in combination with herbal origin garlic protects (100%) against in *in vivo* mouse model of malaria [30]. Studies elsewhere with animal models with artemisinin and curcumin have shown protection against *P. berghei* in resistant strain as well as in cerebral malaria [31]. The protection conferred by most of these artemisinin combinations, as described in above studies, is through various immune responses. The immune responses to malaria differ from other diseases because immunity is only partial in case of malaria whereas it is complete in other viral and bacterial diseases. This leads to difficulties in judging the immune responses that leads to protection.

Discussion

Malaria infection and immune responses are mainly regulated by host responses- innate, adaptive and acquired immunity. It is generally accepted that repeated malaria exposure will lead to increasing

immunity to the disease. Since protection increases with exposure, the acquisition of immunity is faster in high transmission regions where the age group more affected by the disease is infants under one year, who are at higher risk of death. Children born to immune mothers from malaria endemic areas will show passive immunity for 1 or 2 years due to maternal antibodies before they acquire their own active immunity [32-34]. As both age and exposure increase, the individuals also acquire higher ability to limit the consequences of infection, which implies, they are more protected from severe illness and death. However, sterile immunity is seldom attained, as many adults continue to have circulating parasites in the blood [35]. These observations, together with the fact that adult travelers from non-endemic areas are likely to have severe clinical manifestations of the disease, suggest that malaria protection can be immune-mediated. Clinical immunity to malaria could, therefore, be attained when the immune responses are regulated to perform parasite clearance while avoiding detrimental effects and pathology [36]. There are immune mechanisms that effectively act against each parasite.

It is noteworthy to remark that in malaria endemic regions the majority of malaria-infected individuals are also concomitantly infected with a range of other pathogens (bacteria, viruses and protozoans) and the immune responses are different depending on the site of these pathogens, such as intracellular or extracellular. The immune responses also differ such as cellular cytolytic or production of inflammatory cytokines in the first case, whereas in the latter it might be humoral response with the specific immunoglobulins generated to neutralize the pathogen [37], or in some cases such as in malaria parasite, after the combination therapy, both the immune responses might get triggered [28]. Individuals with co-infections can display different abilities in mounting an effective immune response to malaria. It is often observed that immunity to malaria wane quickly when immune adults leave malaria endemic regions, proposing that continued exposure to malaria antigens is necessary not only for the generation of effector and memory cells but also for their persistence. It has been difficult to identify the immune players involved in immunological memory, as these cells are ill-defined in both humans and mouse models by available methods [35].

Immune responses to blood-stage malaria antigens have also memory cells associated with it. However, the normal immune response and memory establishment can be hampered by a chronic malaria infection [35,38]. In fact, the parasite seems to manipulate the host immune system during infection by impairing the generation of immunological memory, which might result in a short-lived memory. Polyclonal activation can also be a strategy of the infectious agents to avoid the host-specific immune responses. It has been debated whether polyclonal activation produces detrimental or beneficial effects in the host [39,40]. Conversely, two potential beneficial effects of polyclonal activation were described. First, by enhancing natural antibodies production, recognizing a conserved range of antigens in many pathogens that can activate the innate immune system via the classical pathways of complement activation. Thus, natural antibodies represent a first line of defense while the adaptive response is not mounted yet [40]. Second, the polyclonal stimuli can be responsible for memory B cells maintenance. In this sense, after in vitro stimulation with polyclonal stimuli, memory B cells proliferate and differentiate into antibody-secreting cells. In the absence of a specific antigen, continuous stimulation and differentiation of these memory B cells have been considered as a reasonable mechanism for the presence of a long-term serological memory [41]. With respect to malaria, it has been debated how malaria antibodies can persist for long period after termination of the infection and the role of polyclonal activation in malaria as to whether does it give rise to long-lived plasma cells [39].

Murine models of malaria have long been used to examine the immune responses to understand the host factors required for malaria protection. Many groups have worked on "Infection and Cure model of malaria" [42] where a virulent, lethal strain *P. berghei* shows resistance to repeated infections by developing immunity, which mimics the results where people who stay in endemic area of malaria will show protection against the disease, even though it takes many years to establish the level of immunity in humans [43]. Whereas in mice, one time infection and drug cure provides long-lasting protection [30,44,45]. Some of the drugs exhibit short-term protection for few days or extend their life span, whereas other drugs in combination show long-term protection, such as curcumin and garlic in artemisinin combination therapy, which needs repeated infections to boost up the immune responses [30,46]. Studies have also shown that infection-induced immunity and cure is possible and long-lasting as seen in case of CBA mice infected with the malaria parasite *P. yoelii* develops a self resolving infection lasting 15-18 days, and thereby suggesting that antibodies produced during adaptive immunity responses is crucial for protection [47]. These data suggest that on recovery from primary infection the hosts are immune to further infection [48].

Conclusion

The outcome of malaria disease is determined by factors, besides the transmission intensity, such as parasite features (virulence, drug resistance), host factors (age, immunity, genetics) and socio-economic factors (access to treatment, politics, gender, economic condition). It is not an individual factor influencing the protection after combination therapy. There have been considerable advances in understanding the mechanism of protection in combination therapy and yet to understand completely what and when (factors) regulates immune pathology. Initial immunological protection could be a general mechanism by which malaria parasites escape from immunological control in successive infections as is frequently observed in high transmission regions. However, there are studies that have established the role of immunity in artemisinin with garlic and curcumin combinations, which show 100% protection. Irrespective of mechanism of action of drugs (towards protection), our concern is to know, once the protection has been noticed, it is for how long? Will protected ones, after malaria therapy, be protected forever? These are the future paths of intensive investigative responses to know the protection after malaria combination therapy, which could lead us a step ahead of immunity. However, if we can remove the interrogative mark, combination therapy makes us hope that it could lead us in developing a vaccine against malaria. No vaccine yet, although groups are working very hard to find it. Recently, renewed calls have been made for better understanding of the cellular and molecular basis of both human and mosquito immune mechanisms in malaria which could lead to focus on eradication program and route to develop the tools for malaria vaccine development.

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