BAOJ Pediatrics

BD Gupta, et al. BAOJ Pediatrics 2018, 4: 2
4: 059

Review

Malaria Vaccine-Current Concept

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Abstract

Malaria is one of the major killing diseases in various parts of world. As a part of development of many ways to control and eradicate this deadly disease one of the novel approach is development of an effective malaria vaccine like there has been vaccines for other infectious diseases. Many vaccines have shown promising results in various trials and RTS,S/AS01 have reached phase 3 as well and will be available for widespread use shortly. But there are concerns regarding development of severe malaria once the immunity of applied vaccine wanes off as there will be no development of natural immunity in vaccinated individuals. For this we need an ideal vaccine which can halt transmission of disease as well provide protection to an individual and the vaccine should also have a long-lasting effect, preferably life-long.

Introduction

Malaria has been amongst one of the major killing disease for long claiming lot of lives world over. Besides deaths it also contributes to maternal anaemia amongst many pregnant women in endemic areas. According to 2016 data, World Health Organisation (WHO) reported approximate 4.29 lacs death per year due to malaria of which more than 90% death were alone from Africa and rest from Asia and South America. Besides, approximately 212 million new cases of malaria every year were estimated by WHO [1,2]. Huge efforts have been made towards controlling this deadly disease through various approaches like developing new insecticides for eradication of mosquito, intensive surveillance activities, and better medicines and so on, but malaria still remains a major problem for many countries of Asia and Africa. One of such approaches has led to think over development of an effective malaria vaccine which can halt the progression of transmission and development of this disease. The Malaria Vaccine Technology Roadmap updated in 2013 has two goals by 2030 (i) to develop a vaccine with >75% efficacy against clinical malaria (ii) to develop vaccines that can reduce transmission of malaria and reduce malaria infection substantially.

Life Cycle of Malaria

Before going into the development of malaria vaccine it is important to know about the life cycle of malaria parasite in short. When an infected female Anopheles mosquito bites a person it injects Plasmodium sporozoites in the blood. These sporozoites reach liver cells and multiply asexually there for 7-10 days during which period person remains asymptomatic. This is called pre-erythrocytic stage. From here the merozoite form of parasite burst into bloodstream starting erythrocytic stage and invade Red Blood Cells (RBCs) where these merozoites multiply till RBC burst, releasing them into bloodstream and reinfecting new RBCs and with this release of merozoites into blood, persons get spikes of fever. Some of these merozoites develop into sexual forms called gametocytes. When a mosquito bites a infected person these gametocytes reach gut of malaria and develop into gametes. Here these gametes form oocyst inside which sporozoites develop and with bursting of oocyst these sporozoites are released which reach salivary glands of mosquito ready to infect a person. This completes the life cycle of plasmodium [3]. Based on this life cycle malaria vaccines have been developed which targets different stages of parasite like pre-erythrocytic, erythrocytic or transmission blocking vaccines.

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Sub Date: March 3rd 2018, **Acc Date**: March 22nd 2018, **Pub Date**: March 23rd 2018.

Citation: BD Gupta, Adarsh Purohit and RK Maheshwari (2018) Malaria Vaccine-Current Concept. BAOJ pediat 4: 059.

Immunology of Malaria

It has been observed that persons residing in areas with high transmission of malaria develop immunity against clinical malaria over a long period of time. They get infected but do not develop disease. The immunity is species specific and it requires repeated exposure to malaria parasite for maintenance of immunity. If such an immune person goes away from such exposure, immunity quickly wanes away and chances of contracting disease increase suggesting that immunological memory against malaria is not very strong. Both humoral as well as cellular response has been reported to be induced after natural malaria infection. As demonstrated in mouse models B-cells and antibodies play an important role in elimination of parasite with some contribution from inflammatory mediators released from macrophages and other immune regulatory cells after T-cell activation. Various proposed effectors mechanism providing immunity against malaria is:

1. Development of antibodies against sporozoites that neutralise sporozoites and prevent invasion of hepatocytes
2. Destruction of intrahepatic parasites mediated by IFN-gamma (interferon-gamma), $CD8^{+}$T-cells and Natural Killer Cells
3. Development of antibodies against merozoites that prevent invasion of RBCs
4. TNF-alpha (Tumour Necrosis Factor-alpha) and IFN-gamma mediated activation of macrophages that kill infected RBCs
5. Antibodies preventing sequestration and maturation of gametocytes

Although the different inflammatory cytokines has been proposed to be protective still there are doubts that whether they have any role in pathology of severe malaria. For example TNF-alpha is thought to be having protective role against malaria infection but there are reports of association of high levels of TNF-alpha with severe malaria and mortality. Similarly level of many proinflammatory cytokines have also been found to be very high in cases with severe malaria. So, the role of these inflammatory mediators remains unclear and it seems that interaction between different pro- and anti-inflammatory cytokines may have a role in pathology of malaria [2,3, 4,5].

Malaria Vaccines

For decades research has been going on development of a safe and effective vaccine against malaria as other measures of controlling malaria transmission has not been effective in eradicating malaria completely. Although natural immunity to malaria develops eventually, but it takes a long time and repeated exposures, during which younger children remain at high risk of severe malaria and mortality. In 1960s it was reported that bites of mosquitoes infected with irradiated sporozoites provide immunity in mice as well as in humans, but it takes repeated bites for immunity to develop. Later on a peptide based vaccine named SpF66 was developed which generated a lot of interest but the results were unsatisfactory so it quickly went into disrepute. Since then researches have been going on to develop a better vaccine and most of the work has been focused on vaccines targeted against pre-erythrocytic stage of malaria parasite. There has also been a renewed interest in whole parasite vaccine as well as on transmission blocking vaccines. Currently many antigens have been identified as target for development of a novel vaccine against malaria. Amongst all the vaccine candidates RTS,S/AS01 is the only one which has cleared phase 3 trials and reached regulatory phase. Besides this other candidates among pipeline which are in phase 2b are ChAd63/MVA ME-TRAP, MSP3, GMZ2 and PfSPZ.

Pre-Erythrocytic (PE) Stage Vaccines

Vaccines acting against this stage of plasmodium target sporozoites and liver stage of parasite and prevent infection from reaching to blood stage. During recent years maximum focus has been on vaccines acting at this stage of malaria parasite as the results have been encouraging in various trials. Vaccine acting at this stage seems promising as this phase lasts 7-10 days giving ample time for elimination of parasite before disease sets in. Besides the number of infected hepatocytes is comparatively lower making it an easy target and also the hepatocytes present the antigens to immune effector cells in a better way in comparison to red blood cells. Earlier the focus was on whole sporozoite vaccine from which it has gradually shifted to subunit vaccines based on various sporozoite antigens. It has also been proposed that even a partially effective PE stage vaccine will reduce the size of inocula and may affect the severity of disease [6,7].

Various antigens as potential vaccine candidates from sporozoites include CSP, LSA-1, SSP2/TRAP and Exp-1. The most advanced amongst all of these is Circum Sporozoite Protein (CSP) based on which RTS,S/AS01 has been developed which has passed phase 3 trials and is being used in selected areas of sub-saharan Africa. CSP is expressed during the sporozoite and liver stage of parasite and plays a role in adhesion of sporozoites and invasion of hepatocytes. Antibodies against CSP have been reported to provide protection by preventing parasite invasion reducing the risk of disease [7,8].

RTS,S/AS01 [2,9,10,11]

It is the most advanced of the vaccine candidates against P. Falciparum malaria. It is a recombinant vaccine against pre-erythrocytic stage of malaria parasite preventing sporozoites from invading liver cells and preventing liver stage development of parasite completely or partially. It is prepared by fusing Circumsporozoite Protein (CSP) with Hepatitis B surface Antigen co-expressed in yeast Saccharomyces cerevisiae. AS01 is used as an adjuvant with liposomes and immunomodulatory molecules MPL and QS-21. The dose which has been used is 0.5 ml of reconstituted vaccine administered intramuscularly (in antero-lateral thigh in 6-12 weeks age group and left deltoid in 5-17 months age group)

The main results of the phase 3 trial were as shown in table 1. The table shows that there was a substantial response to vaccine which was higher in age group 5-17 months then in age group 6-12 weeks, but in both the groups immunity waned off quickly by the end of study and there was some restoration after a 4th dose of vaccine administered after 18 months of third dose. An important point that came out of this study was that there was a rather rebound in cases of severe malaria in subjects who were given 3 doses of vaccine and the benefit of vaccine was nullified by the rather higher number of cases of severe malaria in this group of subjects. This rebound phenomenon has been attributed to the fact that in unprotected individuals there is development of natural immunity with repeated infections over time which protects them from severe malaria, while in vaccinated individuals there was no natural immunity so they became more susceptible for development of severe malaria and at higher risk of morality.

Safety Profile of RTS, S/AS01

It has been found to be safe and effective when administered with other vaccines like DPT, pneumococcal and rotavirus but there have been concerns regarding risk of development of meningitis and febrile seizures in subjects receiving the vaccine. There was a significant higher risk of meningitis in such subjects but is this having a direct causal relationship with the vaccine still needs to be studied. Similarly in age group of 5-17 months there was a rise in cases of cerebral malaria, but its significance to vaccination is still unclear. A hypothetical concern is either this is change in manifestation of disease due to vaccination or may be due to fall in natural immunity because of lack of infection.

Current Recommendations for use of RTS,S/AS01

Based on the data from the Phase 3 trial, WHO does not recommend the use of malaria vaccine in younger (6-12 weeks) age category. Among the older age category (5-17 months), WHO recommends the initial introduction of 4 doses of the malaria vaccine in 3-5 distinct epidemiological settings with high transmission in sub-Saharan Africa. In the phased introduction of the vaccine, Joint Technical Expert Group (JTEG) recommends a three dose initial series of the malaria vaccine with a minimum interval between doses of four weeks, followed by a fourth dose at 15-18 months following the third dose.

Adenovirus (AD35) Vectored CS

RTS,S/AS01 has been shown to induce a strong immunological response via development of anti-CS IgG but CD8+ response is poor to this vaccine. To overcome this a better approach will be combining a vaccine which can produce CD8+ response in a prime-boost sequence with RTS,S/AS01. An adenovirus (Ad35) vectored CS is in developing phase which has shown a better CD8+ response and can be used along with RTS,S/AS01 in future [7,8]

ChAd63-MVA ME-TRAP [7,8,12]

Viral vectors have been shown to be able to induce robust cytotoxic immunity as well as other responses to eliminate malaria parasite infection. Based on this approach chimpanzee adenovirus and modified vaccinia virus Ankara have been used as vectors fused with thrombospondin-related adhesion protein (ME-TRAP) insert and is used in prime-boost sequence to induce immunity against infected liver cells. It is said to generate a better cellular response to liver stage of parasite in comparison to RTS,S/AS01.

Whole Organism Approach-RAS and Sanaria PfSPZ Vaccine [7, 8,13,14,15]

Radiation Attenuated Sporozoites (RAS) has been shown to induce immunity against malaria parasite in various studies over the years. RAS has been shown to induce sterile immunity by mediating CD4+ and CD8+ T-cell dependent mechanisms against antigens expressed by sporozoites and liver stage parasite. Sporozoite-neutralising antibodies also have been proposed to have a role in this protective immunity provided by RAS. Based on the experience that inoculation with radiation attenuated sporozoites may induce protective immunity there has been a renewed interest in metabolically active, non-replicating whole P.falciparum sporozoites (PfSPZ) thawed in liquid nitrogen. It has been shown to induce interferon –gamma and IL-2 responses against sporozoites and infected hepatocytes by CD4+ and γd T cells, but no CD8+ T-cell response. This vaccine is still under clinical development and has shown promising results in volunteers.

Blood Stage Vaccines [4,8,16,17]

Blood stage of malaria parasite has been an attractive target for development of vaccines against malaria, as natural immunity is more targeted against blood stage of parasite. Studies have shown that passive transfer of antibodies (IgG) from malaria-immune adults has been able to mitigate disease in children suffering from malaria. So it has been proposed that if such blood –stage vaccines can be developed which can induce these antibodies then it may prove to be a breakthrough in control of malaria. Various blood stage parasite antigens have been identified as potential vaccine candidates and have been cloned and sequenced so far. Major among them include MSP1 (Merozoite Surface Protein 1), MSP 3 (Merozoite Surface Protein 3), RESA (Ring-Infected Surface Antigen), EBA-175 (Erythrocyte Binding Antigen 175), AMA-1 (Apical Membrane Antigen-1) and SERA-5 (Serine Repeat Antigen).

MSP-1 [8,16,17]

MSP-1 is expressed from the onset of schizogony and plays a role in merozoite invasion of RBCs. Anti-MSP1 antibodies have been associated with decreased risk of clinical malaria. MSP-1 based vaccines have undergone trial in monkey models showing protective immunity but in human trial it has not shown promising results so far.

MSP-3 [8,16]

MSP-3 based vaccines also have been shown to induce protective immunity in monkey models. In phase 1b studies it has shown significant reduction in clinical malaria and is currently under phase2b trial. Another vaccine GMZ2 which is based on combination of MSP-3 and GLURP is also under investigation currently. MSP-3 has been reported to be the most consistent of blood stage antigen associated with development of protective antibodies reducing the risk of clinical malaria.

AMA-1 [8,16]

Apical Membrane Antigen-1 is a blood stage antigen which is expressed during the blood stage of parasite and it helps in invasion of erythrocytes by the merozoites. Antibodies against AMA-1 have been found in persons who have achieved natural immunity against malaria and repeated exposure to malaria generates high titres of antibodies to AMA-1. AMA-1 vaccines are currently undergoing phase 2b studies and have shown some strain-specific protection. Viral vector expressing AMA-1 in prime-boost sequence is also under phase2 studies and have shown to induce strong antibody response.

SERA-5 [8,16]

SERA-5 is expressed during trophozoite and shizont stage of parasite. SE36 is based on SERA-5 antigen and in phase 1 trial it has shown to reduce risk of parasitemia and fever in vaccinated group, but still further trials are needed.

EBA-175 [8,16]

It is a blood stage antigen that helps in binding of merozoites to RBCs. Antibodies against EBA-175 has been shown to reduce parasite growth and inhibition of parasite binding to RBCs in vitro. JAIVAC, a combination vaccine containing MSP-1 and EBA-175 has been undergoing phase 1 trial in India.

Transmission Blocking Vaccines [8,18,19]

This is considered as one of the most novel approaches for malaria eradication. A vaccine which can prevent transmission of malaria parasite may prove to be most critical tool in its eradication. While such a vaccine may not be helpful to the individual in controlling infection and disease but it will be of benefit to the society and prevent other individuals from contracting the disease. By preventing spread of malaria in new individuals it can provide "community immunity" decreasing the total number of malaria cases in the community. Two of the current sexual stage based vaccine projects are working on Pfs25 antigen. Pfs25 conjugated to recombinant Pseudomonas ExoProtein A (EPA) and adjuvanted with alhydrogel has been reported to have antibody response and transmission blocking activity. Pfs230 and Pfs48/45 are other potential candidate antigens for development of TBV.

Conclusion

Most of the existing malaria vaccines are working against single life-cycle stage of malaria parasite but looking at the partial efficacy of such vaccines it would be prudent to develop a combination of vaccines which can act on various stages of plasmodium preventing infection as well as blocking transmission. Secondly, a point of discussion is whether present vaccines will be helpful in reducing mortality due to malaria or rather increase the chance of severe malaria by rebound increase in such cases as there is waning off of immunity provided by vaccines over time and there is no natural immunity in such cases.

Table 1: Results of Phase 3 Trial

	Age group 5-17 months				Age Group 6-12 weeks			
	After2 weeks	After 18 months	At end of study (3 doses)	AT end of study (4 doses)	After 2 weeks	After 18 months	At end of study (3 doses)	At end of study (4 doses)
VE against all episodes of clinical malaria	51.3%	45.7%	26.2%	39%	32.9%	26.6%	18.2%	26.7%
VE against all episodes of severe malaria	44.5%	37.7%	-2.2%	31.5%	38.5%	17.4%	16%	20.5%

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