A step forward in malaria vaccine development

Malaria has remained a major public health concern in the developing world. More than 600 million people are infected annually resulting in more than three million deaths, mostly children in Africa. Increased resistance to malaria drugs has made the situation worse and control of the disease will require rapid development of new control methods, none more important than an efficacious vaccine against malaria. But, given the complexities of the life cycle of malaria parasites, complex host–parasite interactions, polymorphism in most malaria proteins and several mechanisms of evasion of the immune responses in the host by the parasite malaria, vaccine development is a highly complex matter. In fact, many malaria researchers believe that it may not be possible to develop a malaria vaccine at all. Despite these, and other hurdles, there have been serious and sustained efforts to develop malaria vaccine, and several experimental vaccines developed against the three different stages of the parasites life cycle, have been tested in humans, but with limited or no protective ability.

In this context a recently published report of clinical trials with an experimental malaria vaccine in Lancet assumes importance. The report describes safety and immunogenicity of the RTS,S/AS02A candidate malaria vaccine in infants living in a highly endemic area in Africa, in a double blind randomized controlled phase 1/1b study. Earlier trials with this experimental vaccine from Glaxo Smith Kline (GSK) had provided proof of the concept in African children aged between 1 and 4 years which indicated that RTS,S/AS02A provided significant protection against Plasmodium falciparum infections and disease that lasted at least for 18 months post immunization. However, the real targets of a malaria vaccine are the infants, since in malaria-endemic areas children less than 2 years of age are most susceptible to severe disease and death. It is crucial that infants in highly endemic areas are vaccinated against malaria as soon as possible after they are born. The most important and relevant outcome of the recently reported trial is that this vaccine was safely administered to infants.

The RTS,S vaccine comprises of a hybrid protein that contains a C-terminal part of the P. falciparum circumsporozoite protein, including the well-known tetra peptide repeat (NANP), fused to the hepatitis-B surface protein produced along with the hepatitis surface protein in a yeast-based expression system and formulated with a proprietary adjuvant (GSK) called ASO2D. In the reported study carried out in Mozambique under the leadership of Perdo L. Alonzo, 214 infants were enrolled and given three doses of RTS,S/AS02D or a hepatitis-B vaccine (Engerix B) at 10, 14 and 18 weeks of age, along with routine immunization vaccines. During the 6 months of surveillance, there were no more serious adverse events in children with the RTS,S/AS0D than with the hepatitis-B vaccine, which indicated that vaccine formulation was safe in infants. Secondary end-points, in this primarily safety study, included estimation of humoral immune response and investigation of new P. falciparum infections during the third month after the third immunization. A month after the final dose of immunization, a high degree of sero conversion (~99%) was observed in infants who received RTS,S/AS01D vaccine, much higher than with the hepatitis vaccine (20%). However, the antibodies titres achieved by RTS,S immunization have not been reported, perhaps because this was not the primary focus of the study.

Even though protective correlates may not be identifiable at this stage, it is quite clear that the results of immunization studies in children earlier, and now in infants, continue to look promising. Needless to say that the RTS,S-based vaccine will require several more years of clinical studies, perhaps in different locations, before its real promise as an efficacious malaria vaccine is established; but there seems to be enough ground to move on to a phase III trial in children/infants. Further trials, it is hoped, will also address the question of identifying the protection correlates induced upon vaccination with the RTS,S vaccines. Such important information will be useful for further improvement in malaria vaccine design strategies.

Malaria vaccine development is a complex issue and although several vaccine contracts based on the three development stages of the parasite have been taken up for clinical development and trials, they have not provided encouraging leads. The initial success of RTS,S and now in particular its safety and immunogenicity results in infants have provided a much needed boost to malaria vaccine development efforts. Needless to say, there will be increased activity in this field with much more enthusiasm among scientists, and hopefully also in the funding agencies. Finally, there seems to be some light at the end of the long and mostly dark malaria vaccine development tunnel.


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