A Phase I Study of a Candidate Malaria Vaccine

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I. Worldwide Importance of Malaria

Approximately half of the world’s population is at risk for malaria, particularly those living at or near the equator and those in developing nations.

Each year, malaria infects approximately 300 million individuals.

Of these, 1–3 million individuals die, most of whom are under 5 years of age, resulting in one death every 30 seconds.

Most infections occur in regions near the equator – Central and South America, Africa, and Southeast Asia – areas that also contain a large proportion of the world’s population.

In recent years, an increase in anti–malarial drug resistance has complicated both prevention and treatment of the malaria parasite.

II. Life Cycle of Malaria - Opportunities for Prevention

- The Anopheles mosquito is responsible for the development of malaria parasites. Sporozoites from the mosquito travel from the gut to the salivary glands of infected female mosquitoes to the human during a bite.
- Upon entry of sporozoites into the lymphatic system, the malaria parasite (Plasmodium sp.) enters the liver and undergoes amplification.
- These parasites enter the bloodstream and infect red blood cells.
- Parasites mature in the red blood cell and, upon rupture, will either infect additional RBCs or will become gametocytes, capable of being ingested by mosquitoes when another bite occurs.

Therefore, the opportunities to intervene include:

1. Stop mosquito transmission of malaria (mosquito control, use of sleeping nets, insecticides).
2. Increase immunity to the earliest forms of the malaria parasite so that there is no opportunity for amplification in the liver.
3. Increase immunity to the red blood cell forms of the malaria parasite, making further replication ineffective.

III. Study Design

- Multicenter, placebo-controlled, randomized, dosage escalation trial assessing the safety and immunogenicity of four doses (10^8–10^11) of an adenovirus-based circumsporozoite malaria vaccine.
- Healthy adults, 18–40 years of age, with no significant medical problems and no recent or planned travel to malaria endemic regions of the world.
- Vaccine is given on 3 occasions (enrollment, 1 month, 6 months) intramuscularly.
- After each dose, reactogenicity and adverse events are evaluated.
- Starting with the lowest dose, 18 subjects are vaccinated. Subsequent higher doses are not given until the safety of the previous dose is confirmed by an independent Safety Monitoring Committee (SMC).

IV. Challenges with Current Study

- Phase I study: As a result of travel restrictions, stringent laboratory criteria, and subjects’ tolerance of risk, the screening failure has been high. Only 1 in 3 subjects interested in the study remain eligible after screening.
- Initially, extraneous laboratory studies (e.g., obtaining a basic metabolic panel rather than only a sodium concentration) had to be modified so that inappropriate screen failures did not occur.
- During the study, the HIV STEP trial results were released, questioning the safety of an adenovirus–based vaccine vector.
- In addition to halting due to the STEP trial, halting rules for adverse events have been met on multiple occasions, resulting in review of data to ensure subject safety.

V. Conclusions

- Phase I clinical trials are unique in their risk, need for healthy volunteers, and, often, their requirement for dose–escalation to ensure safe doses of the investigational product.
- Attention to detail in protocol development and protocol implementation is critical given that the product has no track record in humans and may, indeed, not be safe.
- Clinical trials must always assess even minor complaints in subjects in order to adequately monitor for safety.
- Despite the lack of malaria in the United States, it is important to conduct trials in healthy adults prior to implementation in other regions of the world.

VI. Acknowledgements

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