Multicentre Phase IIB Trial Design of the GMZ2 Malaria Vaccine

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Abstract

Background: GMZ2 is a blood stage candidate malaria vaccine which comprises a recombinant fusion protein based on conserved fragments of two *P. falciparum* asexual blood-stage antigens, the glutamate-rich protein (GLURP) and merozoite surface protein 3 (MSP3), adjuvanted with Alhydrogel (alum). Phase IA and IB trials have shown good safety and immunogenicity of GMZ2 in malaria-naïve adults as well in African adults and children. The aim of the trial is to assess the efficacy of GMZ2 in African children.

Methods: GMZ2 phase IIB vaccine trial recruited participants in four African countries with various malaria transmission intensities. The trial was not powered to compare efficacy by site but a multicentre approach was chosen to ensure adequate sample size interms of the number of malaria cases and to evaluate safety and immunogenicity in range of settings. Baseline studies were conducted in each trial sites prior to commencement of the trial to pilot surveillance methods and obtain estimates of incidence rates. The study population was children 1-5 yrs of age, to be randomized to receive three doses of GMZ2 or rabies vaccine one month apart. The primary endpoint of the trial is malaria which was defined as tympanic temperature of $\geq 38^0C$ or history of fever in the previous 48 hrs and parasite density of ≥ 5000 /μL, ascertained by Passive Case Detection (PCD) at clinics, over a period up to 6 months after the third dose for the primary analysis, with further follow-up for a total of 22 months.

Conclusion: This is the first multi-country trial of a blood stage malaria vaccine. The trial included substantial capacity development component to establish a multicentre vaccine trial network. The results will guide the further clinical development of GMZ2.

Keywords: Malaria vaccine; GLURP, MSP3, Phase 2 clinical trial, vaccine; GMZ2; Antibody

Introduction

Background

GMZ2 is one of the candidate blood stage malaria vaccine under clinical development [1]. GMZ2 is a recombinant hybrid protein between GLURP and MSP3 expressed in the *Lactococcus lactis* expression system. The candidate vaccine is based on the conserved fragments of the asexual blood stage of the parasite. GMZ2 induced antibodies has been shown to be functional in an ADCC assay [2]. The clinical development has focused on GMZ2/Al(OH)$_3$ formulation due to good safety and immunogenicity profiles in the initial phase I studies [3-

6]. Further it has been demonstrated that GMZ2 adjuvanted in alum elicits antibody titers in humans which are equivalent to those obtained after years of exposure [2]. The GMZ2/Al(OH)$_3$ formulation has so far been tested in three phase I studies: a) a phase IA trial in malaria-naïve German adults [4], b) a phase IB trial in partially immune Gabonese adults [6] and c) a phase IB trial in Gabonese children aged 1-5 years [3]. Each of these trials has shown GMZ2/Al(OH)$_3$ to be safe, well tolerated and immunogenic. The result of a phase IIB study, the design of which is discussed in this article, is published recently [7].

The aim of this phase IIB trial is to assess efficacy. Children between 1-5 years of age are recruited and will receive 3 doses of GMZ2/Al(OH)$_3$ or rabies with one month interval intramuscularly in the right and left deltoid region alternately. Primary end point is efficacy of GMZ2 in preventing clinical malaria over a 6 month period after the last dose. The children will also be followed for a total of 22 months.

Decline in malaria incidence is reported in various countries [8,9]. The decline in malaria incidence could impact the clinical trial result since adequate number of malaria cases is required for statistical analysis. Hence, malaria incidence situation would have an impact on trial design. This paper discusses critical aspects of GMZ2 phase IIB trial design in four East, Central and West African countries. The discussion on trial design facilitates the understanding of the efficacy results of GMZ2 which is already published [7].

Methods

Multicentre design

GMZ2 phase IIB trial recruited trial participants in five sites from four different countries which varied in malaria transmission intensities and patterns. Sites recruiting for GMZ2 were Iganga in Uganda, Sapone and Banfora in Burkina Faso, Lambarene in Gabon and Navrongo in Ghana. Iganga, Uganda has high and all year round transmission with slight variation in intensity while Sapone and Banfora has high but seasonal transmission [10,11]. On the other hand, Lambarene, Gabon has low and all year round transmission with slight difference in transmission intensity while Navrongo, Ghana has low and highly seasonal malaria transmission pattern. Increasing the number of sites was beneficial in ensuring adequate malaria episodes for conclusive statistical analysis. Single centre phase IIB clinical trials have been observed to end up with an inconclusive result due to

drastic decline in malaria incidence (personal communications). In the GMZ2 phase IIB vaccine trial sites are situated in four East, Central and West African countries. With this approach of recruiting in multiple sites with different geographical scenarios it would be very unlikely that the incidence would decline in all the sites at the same time. Safety data would also be acquired from different participants with different genetic background.

From RTS,S trial it was observed that the vaccine protects better in areas of low transmission than it does in high transmission areas [12]. Even if our trial is not powered to compare protection by site, we would still have some information to what extent the vaccine protection differs in low versus high transmission areas.

Baseline studies

Baseline studies were conducted in Burkina Faso, Gabon, the Gambia and Uganda before the commencement of the phase IIB vaccine trial [10,11]. The main purposes of the baseline studies were to acquire information on malaria incidence for sample size calculations and pilot test the surveillance method. The Upper River Region (URR) in The Gambia was initially thought to be one of the clinical trial sites. However, the baseline study conducted in this site in the Gambia indicated that malaria incidence was too low and the site could not recruit for GMZ2 phase IIB trial. Hence, Navrongo, Ghana replaced URR, Gambia.

Case definition of malaria

From the baseline studies it was observed that tympanic temperature of $\geq 38^0C$ or history of fever within 48hrs plus a parasite count of $\geq 5000/\mu L$ has specificity of at least 78% and sensitivity of 56% [11]. The same case definition was employed in all sites, in order to have a specific case definition in all sites recognizing that sensitivity may vary by site. All children with tympanic temperature of $\geq 38^0C$ or history of fever in the previous 48 hours at the time of presentation were screened for malaria. The WHO expert group proposes that fever should be defined as an axillary temperature of $\geq 37.5°C$ in malaria vaccine trials [13]. Axillary measurements, however, may underestimate the core body temperature and hence have low sensitivity whereas tympanic measurement gives a relatively more accurate estimate of the core body temperature [14]. Passive Case Detection (PCD) was preferred over Active Case Detection (ACD) because ACD might under-estimate the effect of a blood stage vaccine, by detecting cases early before they

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develop higher density parasitaemias that the vaccine is expected to prevent.

Timing of vaccine administration

The number of malaria cases that would accrue at the end of this trial was given emphasis in this trial. This is because adequate number of cases is required for appropriate conclusion from statistical analysis. Malaria episodes would significantly increase during peak transmission period in areas with seasonal variation. Hence, in these areas every effort was made to deploy all the three doses of the vaccinations to all participants before the start of peak transmission period. Administration of vaccines in the middle of peak transmission could also result in problems with acquisition of vaccine induced immunity. This could probably be due to heavy sporozoite challenge during peak transmission which would overcome vaccine induced immunity [15,16]. This approach was important to equip study participants immunologically and possibly prevent malaria during the peak transmission period.

Statistical Considerations

Sample size was estimated based on smear positive children from the baseline studies. In Burkina Faso, Ghana and Uganda 30% of children in the control group were estimated to have an episode of malaria (fever or history of fever with parasitaemia ≥ 5000/µL) during the 6 month surveillance period. The estimate for Gabon was that 10% of children would have an episode during the same period of surveillance. Hence total sample size was calculated to be 1840. The sample size gives 90% power to detect a vaccine efficacy of 30% (using significance level of 5%), allowing for 15% loss to follow-up.

If incidence is lower than we have assumed in some or all of the sites, the power will be less. Increasing the analysis period up to a maximum of 12 months may not help very much in terms of power because only one site, Uganda, is likely to yield many additional cases, because of the seasonal pattern of transmission in Burkina Faso and Ghana and the low incidence in Gabon. If incidence in the control group over 6 months is 20% in the three high incidence sites rather than the 30% we have assumed, and 5% in Gabon rather than 10%, the power at 6 months will be about 74% to detect an efficacy of 30%. If incidence is 30% in two sites and 5% in the other two sites, the power is about 78%. If incidence is 10% in three sites and 30% in one site, the power is about 71%. If incidence is 5% in Gabon and 10% in the other sites, the power is only 48% for an efficacy of 30%, but there is 77% power to detect an efficacy of 40%. So with this

sample size in 4 sites we have a reasonable degree of security against the effects of a decline in malaria incidence in our study sites.

In this trial all malaria episodes per child would be considered for primary analysis using Cox regression. Multiple malaria episodes in a child may not be independent to each other and it may be difficult to routinely distinguish between new malaria episodes vs relapse. To avoid bias due to interdependent nature of multiple attacks the Cox regression used a robust estimate of the standard error that takes into account the correlation among multiple observations per child [17]. Malaria symptoms occurring within 14 days of the start of treatment were considered as part of the same episode.

Per protocol analysis of the primary end point would consider all malaria cases recorded right after administration of dose 3. This is, however, unlike other malaria trials where two [18] to four weeks [19] of gap was given between last vaccination and recording of malaria cases. This trial did not allow interval for fear of not accruing enough malaria cases at the end of the trial. It may be argued that the objective of the third dose, the second dose as well, is to induce secondary immune response. This type of response needs shorter time to develop compared to inducing primary immune response [20,21]. However, the induction of secondary immunity still needs few days to develop. Moreover, *P. falciparum* Malaria has also an incubation period of around two weeks. Malaria cases recorded shortly after the last immunization probably started two or more weeks before the third dose administration. Such malaria cases in the GMZ2 group had a probability to be protected by the first two immunizations. But the third immunization would not get a chance to further protect them. A leeway of at least two weeks would have been appropriate and including malaria cases just after the 3rd dose may underestimate the actual vaccine protection.

Working Groups and capacity building

Data Management and Laboratory working groups were established prior to the commencement of the trial comprising of relevant staff from each sites and the sponsor. The working groups met regularly to standardize activities across all sites and provide technical support. Sites differed in their experience in conducting clinical trials and the working groups were used as means of sustained mentorship among the clinical trial sites. Staff exchange programs were also arranged in such a way that young sites would gain considerable experience from experienced clinical trial sites. These

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endeavors resulted in capacity development within participating sites as well as ensured quality of data generated during the trial.

Conclusions

This is a large well powered trial to determine whether GMZ2 can protect children from malaria, and the duration of protection. It will yield information on safety and immunogenicity in children of East, Central and West Africa and from varying epidemiological settings. A multi-centre trial is a complex challenge. There was an emphasis on capacity development, more experienced sites providing technical support to newer sites, and working groups which met regularly to standardize methods.

Acknowledgement

References

1. Schwartz L, Brown GV, Genton B, Moorthy VS (2012) A review of malaria vaccine clinical projects based on the WHO rainbow table. Malar J 11: 11.

2. Jepsen MP, Jogdand PS, Singh SK, Esen M, Christiansen M, et al. (2013) The malaria vaccine candidate GMZ2 elicits functional antibodies in individuals from malaria endemic and non-endemic areas. J Infect Dis 208(3): 479-488.

3. Belard S, Issifou S, Hounkpatin AB, Schaumburg F, Ngoa UA, et al. (2011) A randomized controlled phase Ib trial of the malaria vaccine candidate GMZ2 in African children. PLoS One 6(7): e22525.

4. Esen M, Kremsner PG, Schleucher R, Gassler M, Imoukhuede EB, et al (2009) Safety and immunogenicity of GMZ2 - a MSP3-GLURP fusion protein malaria vaccine candidate. Vaccine 27(49): 6862-6868.

5. Hogenesch H (2012) Mechanism of immunopotentiation and safety of aluminum adjuvants. Front Immunol 3: 406.

6. Mordmuller B, Szywon K, Greutelaers B, Esen M, Mewono L, et al. (2010) Safety and immunogenicity of the malaria vaccine candidate GMZ2 in malaria-exposed, adult individuals from Lambarene, Gabon. Vaccine 28(41): 6698-6703.

7. Sirima SB, Mordmuller B, Milligan P, Ngoa UA, Kironde F, et al. (2016) A phase 2b randomized, controlled trial of the efficacy of the GMZ2 malaria vaccine in African children. Vaccine 34(38): 4536-4542.

8. Aregawi MW, Ali AS, Al-mafazy AW, Molteni F, Katikiti S, et al. (2011) Reductions in malaria and anaemia case and death burden at hospitals following scale-up of malaria control in Zanzibar, 1999-2008. Malar J 10: 46.

9. Karema C, Aregawi MW, Rukundo A, Kabayiza A, Mulindahabi M, et al. (2012) Trends in malaria cases, hospital admissions and deaths following scale-up of anti-malarial interventions, 2000-2010, Rwanda. Malar J 11:236.

10. Kaddumukasa M, Buwembo W, Sekikubo M, Naiwumbwe H, Namusoke F, et al. (2014) Malariometric indices from Iganga, Uganda: baseline characterization in preparation of GMZ2 vaccine trial. BMC Res Notes 7:793.

11. Tiono AB, Kangoye DT, Rehman AM, Kargougou DG, Kabore Y, et al. (2014) Malaria incidence in children in South-West Burkina Faso: comparison of active and passive case detection methods. PLoS One 9(1): e86936.

12. Rts SCTP (2015) Efficacy and safety of RTS, S/AS01 malaria vaccine with or without a booster dose in infants and children in Africa: final results of a phase 3, individually randomised, controlled trial. Lancet 386(9988): 31-45.

13. Moorthy V, Reed Z, Smith PG, Efficacy WHO Study Group on Measures of Malaria Vaccine Efficacy. (2007) Measurement of malaria vaccine efficacy in phase III trials: report of a WHO consultation. Vaccine 25(28): 5115-5123.

14. Erickson RS, Kirklin SK (1993) Comparison of ear-based, bladder, oral, and axillary methods for core temperature measurement. Crit Care Med 21(10): 1528-1534.

15. Eckhoff PA (2012) Malaria parasite diversity and transmission intensity affect development of parasitological immunity in a mathematical model. Malar J 11: 419.

16. Olotu A, Fegan G, Wambua J, Nyangweso G, Awuondo KO, et al. (2013) Four-year efficacy of RTS,S/AS01E and its interaction with malaria exposure. N Engl J Med 368(12): 1111-1120.

17. Cheung YB, Xu Y, Tan SH, Cutts F, Milligan P (2010) Estimation of intervention effects using first or multiple episodes in clinical trials: The Andersen-Gill model re-examined. Stat Med 29(3): 328-336.

18. Rts SCTP, Agnandji ST, Lell B, Fernandes JF, Abossolo BP, Methogo BG, et al. (2012) A phase 3 trial of RTS,S/AS01 malaria vaccine in African infants. N Engl J Med 367(24): 2284-2295.

19. Sirima SB, Cousens S, Druilhe P (2011) Protection against malaria by MSP3 candidate vaccine. N Engl J Med 365(11): 1062-1064.

20. Nossal GJ, Makela O (1962) Autoradiographic studies on the immune response. The kinetics of plasma cell proliferation. J Exp Med 115: 209-230.

21. Vischer TL, Stastny P (1967) Time of appearance and distribution of cells capable of secondary immune response following primary immunization. Immunology 12(6): 675-687.