Trials in Vaccinology 1 (2012) 27–35

Contents lists available at SciVerse ScienceDirect

Trials in Vaccinology

journal homepage: www.elsevier.com/locate/trivac

A review of the tolerability of the candidate TB vaccine, MVA85A compared with BCG and Yellow Fever vaccines, and correlation between MVA85A vaccine reactogenicity and cellular immunogenicity

Rosalind Rowland [a], Nathaniel Brittain [a], Ian D Poulton [a], Angela M Minassian [a], Clare Sander [a], David W Porter [a], Nicola Williams [b], Iman Satti [a], Ansar A Pathan [a,1], Alison M Lawrie [a], Helen McShane [a,*]

[a] The Jenner Institute, Old Road Campus Research Building, Oxford University, Roosevelt Drive, Oxford OX3 7DQ, UK
[b] Centre for Statistics in Medicine, Wolfson College Annexe, University of Oxford, Linton Road, Oxford OX2 6UD, UK

ARTICLE INFO

Article history:
Received 11 May 2012
Revised 11 July 2012
Accepted 16 July 2012

Keywords:
Tuberculosis
Vaccine
MVA85A
Safety
Reactogenicity

ABSTRACT

Background: The development of a new, more effective vaccine against tuberculosis (TB) for use in healthy and HIV-infected adults, children and infants, remains a global health priority. MVA85A is a candidate tuberculosis vaccine designed to enhance immunity to the existing vaccine, Bacillus Calmette-Guerin (BCG). MVA85A entered clinical trials in 2002 and has now progressed to Phase IIb proof-of-concept efficacy trials in infants and HIV-infected adults in Africa.

Methods: A detailed analysis was conducted of the cumulative safety data of intradermal delivery of MVA85A in 112 healthy adult subjects in a series of open label, single arm, non-controlled, Phase I safety and immunogenicity clinical trials in the UK. The trials differed with respect to previous mycobacterial exposure, vaccine regime and dose. Objective safety measures (local reaction size and body temperature) were evaluated for correlations with adaptive antigen-specific immune responses.

Results: All subjects in the combined mid-dose group developed a local reaction, of which 92% were mild, 8% were moderate and no reactions were severe. Around 90% of subjects in each group reported at least one systemic adverse event, most commonly headache, myalgia, malaise, feeling feverish, fatigue and arthralgia. Of all systemic adverse events in the combined mid-dose group, 96% were mild, 3% were moderate and 1% were severe (but none of these were judged to be vaccine-related). Pre-vaccination mycobacterial exposure did not affect the adverse event profile. The size of local reaction and frequency of systemic adverse events increased with MVA85A vaccine dose. There were no documented fevers in the low-dose group, whilst 3% of subjects in the combined mid-dose group and 21% in the high-dose group had documented fevers. Peak local reactions were larger after a second poxvirus vaccination, but other local and systemic adverse events were comparable to a single MVA85A vaccination. No severe systemic AEs or serious adverse events in any group were judged to be vaccine-related. Local AEs compared favourably to BCG vaccine-induced local AE and systemic AEs after MVA85A vaccination were comparable to those after the live viral Yellow Fever vaccine in similar populations. There were no correlations found between local reaction size or body temperature and adaptive immune responses (measured by *ex vivo* interferon gamma Enzyme Linked Immunospot).

Conclusions: The candidate TB vaccine, MVA85A has been safely administered to over 100 healthy adults in the UK. Intradermal vaccination with MVA85A induced a transient, superficial reaction local to the injection site and mild short-lived viral symptoms. The local and systemic AE profile of MVA85A vaccination was comparable to published data of other intradermal vaccines and live viral vaccines respectively. Local reaction sizes and body temperature measurements did not correlate with the adaptive cellular immune response to MVA85A.

* Corresponding author. Tel.: +44 01865 617606; fax: +44 01865 857471.
E-mail address: helen.mcshane@ndm.ox.ac.uk (H. McShane).

[1] Present address: Centre for Infection, Immunity and Disease Mechanisms, Biosciences, School of Health Sciences and Social Care, Brunel University, Uxbridge, Middlesex UB8 3PH, UK.

1879-4378
http://dx.doi.org/10.1016/j.trivac.2012.07.001

1. Introduction

Tuberculosis (TB) is one of the leading global causes of death and disability from a single infectious agent, *Mycobacterium tuberculosis* (*M.tb*), with an estimated 8.8 million new infections and 1.5 million deaths in 2010 [1]. The Stop TB Partnership goals include reducing the global burden of TB (prevalence and death rates) by 50% by 2015 compared to 1990 levels and eliminating TB as a public health problem by 2050. Prophylactic immunization is a key strategy in reducing the incidence of TB. *Mycobacterium bovis* Bacillus Calmette-Guerin (BCG), the only licensed TB vaccine, is given in mass immunisation campaigns to neonates in high-risk populations as part of the WHO Expanded Programme on Immunisation (EPI). BCG consistently protects against TB meningitis and disseminated TB in children but its efficacy wanes with time [2–4]. In addition, BCG affords highly variable protection against pulmonary disease, which accounts for the burden of global TB mortality and morbidity [5]. A new, more effective TB vaccine is a major global health priority. A feasible and promising strategy is for a new prophylactic vaccine to be given in a regime which includes BCG, in order to enhance the immunity afforded by BCG.

We are developing a subunit viral-vectored vaccine, using Modified Vaccinia Virus Ankara (MVA) as a delivery system for the mycobacterial antigen 85A. This candidate vaccine is designated MVA85A and has been evaluated in a series of small Phase I safety and immunogenicity clinical trials in the UK since 2002 [6–9]. The promising safety and immunogenicity of MVA85A led to further clinical trials in target populations in South Africa, The Gambia and Senegal [10–15]. Two proof-of-concept (Phase IIb) efficacy trials are now underway in BCG-vaccinated South African infants and HIV-infected African adults. As the early UK trials had small group sizes (typically 12 subjects), only very common adverse events (AEs) were detected by individual trials. Now that over 100 healthy adult subjects in the UK have received MVA85A vaccination, we have the opportunity to perform an integrated further evaluation of the cumulative safety and tolerability of MVA85A vaccination in a larger cohort.

2. Subjects and methods

2.1. Clinical trials

Safety data from seven open label, single arm, non-controlled safety clinical trials were analysed (Table 1) [7–9,16,17] (Porter, unpublished data). The trial protocols all received full ethical approval from the Oxfordshire Research Ethics Committee (OXREC) or the Gene Therapy Advisory Committee. Regulatory approval for these studies was granted by the Medicines and Healthcare products Regulatory Agency (MHRA), UK.

2.2. Location

The trials were conducted at the Centre for Clinical Vaccinology and Tropical Medicine, Churchill Hospital, Oxford and were sponsored by the University of Oxford. Northwick Park Hospital, London was used as a second site for recruitment and follow up of *M.tb*-infected subjects [7].

2.3. Subjects

Healthy adult subjects between the ages of 18 and 55 years were recruited from the Oxford region and, for latently *M.tb*-infected (LTBI) subjects, from TB contact clinics in Oxford and London [7]. Fully informed written consent was obtained from all subjects prior to any study procedures being performed. Before enrolment, all subjects underwent medical screening, which included medical history, physical examination, urinalysis and blood tests. Specific exclusion criteria included significant allergy; immunosuppression; clinically significant past or current medical history; psychiatric disorders; injecting drug use or excess alcohol use; confirmed or planned pregnancy; and any previous MVA or Fowlpox (FP9) vaccinations. Subjects with clinically significant abnormalities in their routine haematology, biochemistry or urinalysis results, or infection with human immunodeficiency virus (HIV), hepatitis B virus (HBV) or hepatitis C virus (HCV) were also excluded. Subjects were required to consent to refrain from blood donation throughout the trials and females were required to use continuous effective contraception.

2.4. MVA85A

The construction of MVA85A has been described previously [18]. Clinical grade MVA85A (batch number 010402) was manufactured to Good Manufacturing Practice standard by IDT Biologika GmbH (Dessau, Germany). MVA85A was administered by intradermal injection into the deltoid area of the arm on the day of vaccination at doses of 1×10^7 plaque forming units (pfu) (low-dose); 5×10^7 pfu (mid-dose) or 1×10^8 pfu (high-dose) (Table 1). The low and mid-dose vaccinations were administered as a single intradermal injection. The high-dose vaccinations were administered as two injections, each a dose of 5×10^7 pfu, delivered simultaneously one into each arm.

2.5. Enrolment and follow up

Subjects received their first MVA85A vaccination on the day of enrolment and were followed up for 24 or 52 weeks following vaccination, depending on the individual trial protocol.

Table 1
Demographics of subjects vaccinated with MVA85A in the UK according to group.

Group	Vaccine dose (pfu)	*N*	Males (%)	Median age (range) (years)	Clinicaltrials.gov reference and citation
M[a]	5.0×10^7	14	5 (36)	29 (19–54)	NCT00423566 [9]
MM[b]	5.0×10^7	11[a]	5 (45)	31 (20–48)	NCT00423566 [9]
BM[c] low-dose	1.0×10^7	12	4 (33)	27 (21–42)	NCT00465465 [17]
BM mid-dose	5.0×10^7	43	17 (40)	26 (23–54)	NCT00427453 [8] NCT00427830 [9] NCT00653770 [16]
BM high-dose	1.0×10^8	24	11 (46)	24 (19–32)	NCT00465465 [17] NCT00548444 (Porter, unpublished data)
LTBI[d]	5.0×10^7	12	10 (83)	31 (20–49)	NCT00456183 [7]
BFM[e]	5.0×10^7	7	3 (43)	30 (24–47)	NCT00653770 [16]

[a] M = single vaccination with MVA85A.
[b] MM = Two sequential vaccinations with MVA85A (of the 14 subjects vaccinated with MVA85A, 11 subjects received a second MVA85A vaccination after an interval of 4 weeks within the same clinical trial).
[c] BM = single vaccination with MVA85A in previously BCG-vaccinated subjects.
[d] LTBI = Latent *M.tb* infection (10 of the 12 subjects had evidence of prior BCG vaccination).
[e] BFM = Sequential vaccination with FP85A, followed by MVA85A after an interval of 4 weeks in previously BCG-vaccinated subjects.