Vaccine xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Vaccine

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

Conference report

Correlates of protection for enteric vaccines

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ARTICLE INFO

Article history:
Received 19 January 2017
Received in revised form 4 April 2017
Accepted 3 May 2017
Available online xxxx

Keywords:
Enteric vaccines
Enteric pathogens
Correlates of protection
Conference

ABSTRACT

An immunological Correlate of Protection (CoP) is an immune response that is statistically interrelated with protection. Identification of CoPs for enteric vaccines would help design studies to improve vaccine performance of licensed vaccines in low income settings, and would facilitate the testing of future vaccines in development that might be more affordable. CoPs are lacking today for most existing and investigational enteric vaccines. In order to share the latest information on CoPs for enteric vaccines and to discuss novel approaches to correlate mucosal immune responses in humans with protection, the Foundation Mérieux organized an international conference of experts where potential CoPs for vaccines were examined using case-studies for both bacterial and viral enteric pathogens.

Experts on the panel concluded that to date, all established enteric vaccine CoPs, such as those for hepatitis A, Vi typhoid and poliovirus vaccines, are based on serological immune responses even though these may poorly reflect the relevant gut immune responses or predict protective efficacy. Known CoPs for cholera, norovirus and rotavirus could be considered as acceptable for comparisons of similarly composed vaccines while more work is still needed to establish CoPs for the remaining enteric pathogens and their candidate vaccines.

Novel approaches to correlate human mucosal immune responses with protection include the investigation of gut-originating antibody-secreting cells (ASCs), B memory cells and follicular helper T cells from samples of peripheral blood during their recirculation.

1. Introduction

An immunological Correlate of Protection (CoP) is an immune response that is statistically interrelated with protection and may be either a mechanistic CoP (mCoP) or a non-mechanistic CoP (nCoP) [1]. There may be more than one CoP for a disease, which are usually referred to as «co-correlates» [2]. Most currently known CoPs relate to neutralizing serum or mucosal antibody, but other functions of antibody may be more important in particular cases. In addition, cellular immune responses often synergize with antibody to protect.

Vaccines are licensed against some enteric pathogens and several candidate vaccines against other pathogens are in development or testing. For most both existing and not yet licensed enteric vaccines, established CoPs are lacking today. To examine correlates of enteric vaccine-induced protection, the Fondation Mérieux organized a conference from March 21–23 2016 (“Les Pensières” Conference Centre, Annecy-France). The purposes of this workshop that gathered immunologists, epidemiologists, statisticians, infectious disease and regulatory experts were to provide state of the art information on CoPs for enteric vaccines and to discuss novel approaches to correlate mucosal immune response with protection in humans.

Key note introductory lectures by *Stanly Plotkin* (University of Pennsylvania, USA) and *Jan Holmgren* (University of Gothenburg, Sweden) set the scene for the conference by summarizing current

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http://dx.doi.org/10.1016/j.vaccine.2017.05.005

knowledge on "CoPs induced by vaccines with special reference to enteric vaccines" and "The links between mucosal and systemic immunity: what is known and what is not known". Enteric pathogens differ in the way they cause infection and disease, especially whether they are invasive or not and to which extent they cause mucosal inflammation. This influences what type of immune responses they elicit, how vaccination by different routes may protect, and what immune CoPs there may be. Second generation enteric vaccines that could be cheaper, more protective and possibly need only a single dose are under development. Evaluation of these new generations of vaccines which might be preferred to the existing vaccines may encounter ethical objections to future placebo-controlled efficacy trials in endemic populations. Identification of a CoP could facilitate a non-inferiority study to support licensure. It would also help design lower sample size studies to better understand the sometimes large variation in vaccine efficacy in different settings and the effect of interventions to improve vaccine performance in low income settings. The finding of a CoP would also facilitate the testing and licensure of future vaccines that might then be faster, more affordable and could help increase the global vaccine supply especially in developing countries. Some of these aspects were also addressed by *Nicholas Grassly* (Imperial College of London, the UK) who discussed how experiences from use of CoPs in polio vaccination might apply to other enteric vaccines.

The prioritization of enteric vaccine candidates requires a better understanding of the incidence, etiology, and adverse clinical consequences of the most life-threatening and disabling episodes of diarrhea among young children. Karen Kotloff (University of Maryland, USA) reviewed the main findings of the Global Enteric Multicenter study (GEMS), a prospective, age-stratified, matched case/control study of moderate-to-severe diarrhea (MSD) in children aged 0–59 months in Africa and Asia [3]. This study found that most attributable cases of MSD were due to five pathogens: rotavirus, *Cryptosporidium, Shigella,* heat-stable enterotoxin (ST)-producing Enterotoxigenic *Escherichia coli* (ETEC), and to a lesser extent Adenovirus 40/41. *Campylobacter jejuni*, Aeromonas and *Vibrio cholerae* O1 had regional importance (and it should be noted that especially *V. cholerae* continues to be an important pathogen responsible for many deaths in children above age 5 years and adults). Reanalysis of original samples by quantitative molecular diagnostic approach based on real-time PCR, led to revised estimates of the most important causes of MSD which were now in descending order, *Shigella* spp, rotavirus, adenovirus 40/41, ST-producing ETEC, *Cryptosporidium* spp, and *Campylobacter* spp [4]. These results suggest that targeted interventions for a limited number of pathogens, e.g. in the form of vaccines, might have a substantial impact.

2. Case studies of correlates of protection

Established and/or possible new CoPs for a number of existing or in-pipeline vaccines against important enteric infections/-pathogens were specifically addressed.

2.1. Bacterial pathogens

2.1.1. Cholera

The causative agent of cholera, *V. cholerae*, is a non-invasive pathogen causing severe and often life-threatening diarrhea through the action on the small intestinal epithelium of the cholera enterotoxin released by the bacteria during their extensive multiplication in the intestine [5,6]. Of >200 *V. cholerae* serogroups, serogroup O1 (with two major serotypes, Inaba and Ogawa) currently causes >99% of all cholera cases globally.

Knowledge gained by challenged volunteer model studies regarding immune protection in cholera and immune response to oral cholera vaccines (OCVs) were reviewed by *Myron Levine* (University of Maryland, USA). Such studies were successful in predicting the substantial protection afforded by killed whole cell OCVs in phase 3 clinical trials [8,9] suggesting that this challenge model could serve as surrogate for field evaluation. However, the protective efficacy induced by a single-dose live, attenuated OCV (CVD-103HgR) observed in human challenge studies [10–12] was not reproduced in a placebo-controlled large field trial [13]. This discrepancy may reflect differences in microbiota and preexisting immune exposure between cholera endemic and non-endemic populations, both factors being likely to have a greater impact on the immunogenicity of a live as compared to a killed OCV. Further work, ideally also evaluating the model in a cholera endemic setting, is needed before the challenged human volunteer model can be used as a reliable surrogate for field evaluation of OCVs.

Serological studies have shown an inverse relationship between naturally acquired serum vibriocidal antibody titer and susceptibility to cholera infection [14,15]. In human challenge studies, almost 100% of challenged volunteers who developed clinical illness mounted strong serum vibriocidal antibody responses which were largely IgM. The titers peaked very early and fell towards baseline between one and 6 months post-challenge but remained above pre-challenge levels [16]. The usefulness of serum vibriocidal antibody seroconversion as a CoP has been recently investigated in a human cholera challenge model that showed strong correlation between serum vibriocidal antibody seroconversion and protection against severe and mild cholera in vaccinees challenged at 10 days or 3 months post-vaccination [10]. However, as mentioned the protective effect of a single dose of live oral cholera vaccine (CVD-103 HgR) observed in human challenge studies [10–12] was not confirmed in a placebo-controlled field efficacy trial [13]. Hence, the utility of serum vibriocidal antibody as a proxy in assessing the protective efficacy of cholera vaccines is not demonstrated at a trial aggregate level and may need separate evaluation in cholera endemic settings.

John Clemens (International Centre for Diarrheal Disease Research, Bangladesh) discussed CoPs based on knowledge of the immune response induced by cholera vaccines and he also suggested novel types of studies for licensure of new OCVs. Parenteral cholera whole cell vaccines were developed soon after the isolation of the pathogen but were withdrawn in the 1970s due to their reactogenicity and limited and transient protection. Oral ingestion of antigens has been found to be the most effective method of eliciting mucosal immunity and immune protection. The latter is mediated by mucosal secretory IgA (SIgA) antibodies produced locally in the intestine that are primarily directed against the cell wall lipopolysaccharide (LPS) and/or the binding (B subunit) part of cholera toxin (for a recent review see [6]). In accordance with this, the incidence of cholera in breast-fed infants and children in Bangladesh was inversely correlated to the levels of SIgA anti-LPS and anti-cholera toxin B subunit antibodies (both independently and when they were combined synergistically) in their mothers' breast-milk [7]. Since intestinal SIgA levels induced by OCVs vane within the first year after cholera infection or OCV immunization but significant protection lasts for several years, the development of immunologic memory that can be activated into renewed protective SIgA production upon exposure to cholera pathogen is pivotal; consistent with this Swedish volunteers who received initial immunization with two doses of OCV displayed a strong anamnestic SIgA response when exposed to a single low-dose booster immunization as late as >10 years after the initial immunizations [17]. Currently, three WHO-prequalified OCVs are available, all of which are based on killed *V. cholerae* O1 Inaba and Ogawa cholera

Please cite this article in press as: Holmgren J et al. Correlates of protection for enteric vaccines. Vaccine (2017), http://dx.doi.org/10.1016/j.vaccine.2017.05.005