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Norovirus vaccines under development

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ABSTRACT

Noroviruses (NoVs) are one of the leading causes of acute gastroenteritis, including both outbreaks and endemic infections. The development of preventive strategies, including vaccines, for the most susceptible groups (children <5 years of age, the elderly and individuals suffering crowding, such as military personnel and travelers) is desirable. However, NoV vaccine development has faced many difficulties, including genetic/antigenic diversity, limited knowledge on NoV immunology and viral cycle, lack of a permissive cell line for cultivation and lack of a widely available and successful animal model. Vaccine candidates rely on inoculation of virus-like particles (VLPs) formed by the main capsid protein VP1, subviral particles made from the protruding domain of VP1 (P-particles) or viral vectors with a NoV capsid gene insert produced by bioengineering technologies. Polivalent vaccines including multiple NoV genotypes and/or other viruses acquired by the enteric route have been developed. A VLP vaccine candidate has reached phase II clinical trials and several others are in pre-clinical stages of development. In this article we discuss the main challenges facing the development of a NoV vaccine and the current status of prevailing candidates.

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1. Introduction

Norovirus (NoV) belongs to the genetically diverse RNA virus family Caliciviridae, which includes another human calicivirus, Sapovirus, and animal caliciviruses (Lagovirus, Vesivirus and Nebovirus) [1]. NoV was first linked to human disease in 1972, when viral particles were identified by immune electron microscopy in stool samples from adult volunteers who had been inoculated with stool filtrates obtained from individuals who contracted gastroenteritis during a 1968 outbreak in Norwalk, Ohio that affected schoolchildren, teachers and associated household members [2,3]. Volunteer challenge studies proved the causal role of these round, rough-surfaced particles, which were named the Norwalk agent (prototype of the current *Norovirus* genus). Many similar small, round-structured viruses (SRSVs), also referred to as caliciviruses at that time due to their cup-shaped appearance by electron microscopy, were described in subsequent outbreaks of gastroenteritis and in children with sporadic acute diarrhea [2,4].

Initial studies based on virus identification in stool by electron microscopy and seroprevalence determination, indicated that these viruses were a relevant cause of acute gastroenteritis outbreaks worldwide [4–6]. Sequencing of the full Norwalk virus genome in the 1990s represented a milestone, allowing, among other advances, comparative genetic studies between the various known caliciviruses [7]. Further, developments in molecular biology technology allowed for the synthesis of virus like particles (VLPs) and antisera, which were used for antigenic comparison, antigen detection in stools and seroprevalence studies [5,8,9]. These breakthroughs lead to significant advances in our knowledge on viral taxonomy and on the epidemiology of calicivirus infections in humans and animals. However, due to the fact that researchers have been unable to develop permissive cell lines for NoV culture and that successful animal models have been extremely difficult to develop, advances in our understanding of the viral cycle, as well as the development of antiviral drugs, has been minimal [10,11].

Currently, NoV infections are considered a significant public health problem worldwide [12,13]. A recent World Health Organization systematic review estimated 124,803,946 cases (95%CI: 70,311,254–251,352,877), accounting for the loss of 2,496,078 disability-adjusted life years (DALYs; 95%CI: 1,175,658–5,511,092) and 34,929 deaths (95%CI: 15,916–79,620) annually [12]. Disease impact has been recognized in 4 clinical

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settings: food/waterborne gastroenteritis outbreaks affecting all ages, acute endemic diarrhea in children, acute endemic diarrhea in adults and gastroenteritis in immunocompromised patients [9,14]. NoV is the most common agent causing food/waterborne gastroenteritis outbreaks. It accounts for 30–80% of outbreaks, and occurs in a variety of closed settings, including schools, day care centers, healthcare facilities, hotels, restaurants and ships, among others [15–18]. NoV is the second leading cause, after rotavirus, of acute endemic diarrhea in children, accounting for 10–20% of associated hospitalizations and emergency room visits in middle/high income countries [19–22] and 1–15% in low income countries [13,22–24]. NoV is becoming the main cause of gastroenteritis in children in countries that have implemented rotavirus vaccines [25–27]. NoV has also recently been recognized as a significant cause of acute endemic gastroenteritis in adults, accounting for 5–15% of cases [28–30]. Among adults, the elderly population is the most susceptible to severe infection, which can be accompanied by severe dehydration requiring ICU admission, and in some instances death [30]. A recent study in the United Kingdom reported a significantly higher incidence of NoV infection in children <5 years of age as compared to other age groups (142.6 vs. 37.6 cases per 1000 person-years). This study also reported that general practice consultations associated with NoV infection were 12 times higher in children <5 years of age as compared to other age groups, and that there were twice as many NoV cases in adults >65 than in adults 15–64 years of age [29]. Among immunocompromised patients, mainly bone marrow and solid organ transplant patients, NoV can cause more severe and/or prolonged gastroenteritis episodes [31,32]. Regardless of age, the severity of NoV clinical manifestation varies greatly, from asymptomatic infection to severe gastroenteritis accompanied by dehydration and even death in susceptible individuals.

The epidemiological burden of NoV, as outlined above, is significant, and underscores the need for appropriate preventive strategies. Vaccine development is the cornerstone for prevention, aiming to decrease the burden of NoV-associated gastroenteritis mainly in the most susceptible groups, children <5 years of age, the elderly and individuals experiencing crowding conditions, such as military personnel and travelers.

2. Virological characteristics

NoVs are non-enveloped viruses with a positive-sense, polyadenylated, single-stranded RNA genome of approximately 7,500 nucleotides in length. Typical NoV virion particles are 40 nm in diameter and have an icosahedral symmetry, conformed by 90 dimers of the main structural protein, VP1 [33]. VP1 is a 60-kDa protein that has two domains (S and P) linked by a hinge. The S domain is responsible for the shell structure of the capsid, and the P domain protrudes from the shell, generating spikes that denote the characteristic "cup-like" depressions that give name to this family [33,34]. The P domain allows binding to histoblood group antigens (HBGA) on the surface of host cells and confers antigenic variability [35].

Genomic RNA is organized into 3 open reading frames (ORFs): ORF1 encodes a polyprotein cleaved by a viral protease during replication into a set of non-structural proteins, ORF2 encodes the main capsid protein (VP1), and ORF3 encodes a minor structural capsid protein (VP2) [36,37].

NoVs are genetically and antigenically diverse, due to frequent point mutations and recombination events [38–40], and are currently grouped into 6 genogroups, of which three (GI, GII and GIV) have been associated with human gastroenteritis [41]. The original Norwalk virus, which has received the majority of research effort related to serological and blocking assays, belongs to genogroup I (GI.1). Since its discovery, over 25 genotypes have been reported within these 3 genogroups affecting humans; nevertheless, worldwide GII.4 is by far the most predominant [22,42,43].

3. Considerations for the development of a NoV vaccine

NoV vaccine development has been considered difficult for many reasons. First, immunity against NoV seems complex, including both cellular and humoral immune components. Major advances in understanding the underlying immune mechanisms of infection have been difficult, due to the lack of permissive cell lines for culture [44] and/or of a widely available and successful animal model [10,11]. Although viral neutralization assays have not been possible, due to the lack of an adequate cell culture system, HBGA blocking assays and hemagglutination inhibition assays strongly suggest that natural infections are followed by the production of genogroup-specific protective antibodies [45,46].

Second, immunity to natural NoV infections seems to be short lived, lasting at most a few years. Volunteer and clinical studies demonstrated that 2–3 weeks after a NoV infection, serum specific antibodies could be detected, and that they persisted for many months [47,48]. Adults who were re-challenged with the same strain shortly after initial exposure (6–14 weeks) were protected, but if the exposure took place 2–6 years after the first challenge, they were able to be symptomatically reinfected [9,49]. Importantly, the viral dose given to volunteers in early adult challenge studies was several logs greater than naturally occurring infective doses, and thus may not actually represent the natural phenomenon of infection and immunity [50]. Thus, despite the fact that these results suggested at best short-lived protection in adult challenge studies, posterior considerations have lead researchers to postulate that true protection associated with natural infections may be different (i.e. more prolonged), especially during childhood.

In children, there is evidence suggesting that repeated infections are common, but that a previous infection with a given genogroup confers protection against symptomatic reinfection when reexposed to a virus from the same genogroup [21,51]. O'Ryan et al. reported in a cohort study of Chilean newborns followed with monthly stool testing for NoV for 18 months, that more than a half of the children had NoV infections, the majority of which were asymptomatic; reinfections were frequent, but the majority were asymptomatic. Symptomatic cases associated with GII genotypes occurred only as a primary infection or when preceded by a non-GII genotype infection [21]. These data suggest that a prior infection with a homotypic genogroup could be protective against new symptomatic episodes, indicating that a vaccine could be effective. These findings were consistent with those of a Peruvian child cohort study [51] and the MAL-ED multinational cohort study [52], who also observed that prior infection was protective against later symptomatic infections. However, conclusions emerging from an Ecuadorian cohort study [53] were contradictory, indicating that previous NoV infections did not play a clear protective role against future NoV infections. This conclusion was based on the fact that the relative risk that a GI or GII infection represented a reinfection (secondary, terciary, etc.) with the same genogroup, as compared to children having no documented previous infection, was close to 1. One possible limitation of this study was that by design it had a lower frequency of stool sample collection than the Chilean cohort, every 6 months versus monthly, which may have led to underestimating the incidence of prior asymptomatic NoV infections. Additionally, the data did not differentiate between asymptomatic and symptomatic NoV infections; thus it is not possible to determine if a first infection conferred protection against later symptomatic infections. Importantly, data from this cohort did show a clear pattern of reduced NoV infections with increasing

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