Review

Prospects and Challenges in the Development of a Norovirus Vaccine

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ABSTRACT

Purpose: Norovirus is the leading cause of acute epidemic gastroenteritis among children under the age of 5 years and adults in the United States and in adults worldwide, accounting for an estimated 20% of episodes of acute gastroenteritis across all ages. No effective vaccine is presently available. This article provides an overview of the current state of norovirus vaccine development, emphasizing barriers and challenges in the development of an effective vaccine, correlates of protection used to assess vaccine efficacy, and the results of clinical trials of the major candidate vaccines.

Methods: We performed an unstructured literature review of published articles listed in PubMed in the field of norovirus vaccine development, with an emphasis on studies in humans.

Findings: Two candidate vaccines have reached clinical trials, and a number of other candidates are in the preclinical stages of development. Multivalent vaccination may be effective in inducing broadly neutralizing antibodies protective against challenge with novel and heterologous norovirus strains. Most identified correlates of protection have not been validated in large-scale challenge studies, nor have the degrees to which these correlates covary been assessed.

Implications: Immune correlates of protection against norovirus infection need to be further developed to facilitate additional studies of the tolerability and efficacy of candidate norovirus vaccines in humans. (*Clin Ther*. 2017;39:1537–1549)

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INTRODUCTION

Norovirus is the leading cause of epidemic acute gastroenteritis in children and adults in the United States, resulting in 19 to 21 million episodes of illness, 1000 reported outbreaks, 2 million office visits, 70,000 hospitalizations, and up to 800 deaths in the United States each year, with up to 50% increases in these numbers during years in which a new pandemic strain emerges.[1,2] Findings from surveillance studies suggest that norovirus causes ~20% of acute gastroenteritis in US children under the age of 5 years, that the rate of norovirus gastroenteritis in this age group now exceeds that of rotavirus gastroenteritis, and that norovirus gastroenteritis incurs an estimated US $273 million in treatment costs each year.[3,4] Globally, norovirus causes an estimated 699 million illnesses and 219,000 deaths each year, representing one fifth of episodes of acute gastroenteritis across all ages and resulting in >$4 billion in direct medical costs and >$60 billion in indirect societal costs, the latter of which are overwhelmingly due to lost productivity.[5,6] Rates of illness requiring medical care and mortality rates are particularly high among children under the age of 5 years and adults aged >65 years, respectively.[1]

Given this burden of illness, analyses modeling cost-effectiveness and economics of a norovirus vaccine are unsurprisingly favorable. Bartsch et al[7] demonstrated that vaccinating 95% of the US population with a human norovirus vaccine costing $25 and conferring protection from norovirus in 75% of recipients for at least 48 months would have the potential to reduce net health care expenditures in the United States by up to $2.1 billion, while also preventing >2 million episodes of norovirus gastroenteritis each year. Based on the cost of the vaccine, the percentage of vaccine recipients protected, and the duration of protection conferred, the cost per case averted varied significantly, from –$303 to $3315. Tallant et al[8] estimated that vaccinating US troops against norovirus would either be cost-neutral or possibly cost-saving and could be more cost-effective than vaccination against common bacterial causes of gastroenteritis. With the potential to reduce overall health care costs while preventing a significant burden of disease, norovirus is an attractive target for vaccine development.

We review the current status of and existing challenges in the development of an effective norovirus vaccine, describe meaningful correlates of protective efficacy for norovirus vaccine candidates, and examine the status of the major norovirus vaccine candidates presently in development.

MATERIALS AND METHODS

We performed an unstructured literature review of published articles listed in PubMed in the field of norovirus vaccine development, with an emphasis on studies in humans.

RESULTS

Norovirus Virology and Possible Barriers in the Development of an Effective Norovirus Vaccine.

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Noroviruses are single-stranded RNA viruses in the family *Caliciviridae* and are classified into seven genogroups based on phylogenetic analysis of the entire virus genome or of individual virus genes. Genogroups I and II (GI and GII) are the most prevalent causes of norovirus infection in humans (Table I). Each genogroup is subclassified into genotypes based phylogenetic analysis of capsid (Figure) and polymerase gene sequences.[9] Mutations as well as recombination within and between norovirus genotypes in co-infected patients have led to the periodic emergence of new norovirus variants as well as broad genetic and antigenic diversity of circulating norovirus strains. This genetic diversity poses a potential challenge in the development of broadly protective norovirus vaccines, as the findings from some studies have shown that immunization and natural infection with a norovirus may elicit immunity specific to the genogroup of that norovirus.[10,11] The emergence of GII genotype 4 (GII.4) variants that have caused new global pandemics suggests that evolution of the capsid gene can help the virus to escape a host's immunity induced by infection or vaccination.[12] However, findings from serologic studies have shown that many individuals have cross-reactive, putatively protective serum antibodies that recognize new norovirus variants years before such variants emerge.[13,14] GII noroviruses cause >90% of norovirus disease in the United States, with GII.4 noroviruses causing 50% to 80% of disease from year to year.[2] Accordingly, while some of the early efforts to develop norovirus vaccines were based solely on the first discovered human norovirus, GI.1, vaccine-development efforts have been directed toward GII.4 noroviruses, with or without the inclusion of a GI norovirus antigen.

Table I. Genogroups and genotypes associated with norovirus infection in humans.

Genogroup	Genotypes
I	GI.1–GI.9
II	GII.1–GII.10, GII.12–GII.17, GII.20–GII.22
IV	GIV.1

The norovirus genome contains 3 open reading frames that encode a large polyprotein encompassing the nonstructural norovirus proteins, the major norovirus capsid protein VP1, and a minor stabilizing protein VP2.[15] Norovirus VP1 contains a highly conserved shell (S) domain stabilizing the icosahedral structure of the viral particle, and a variable protruding (P) domain, which is composed of a moderately conserved P1 subdomain and a highly