JCI insight

CLINICAL MEDICINE

Safety and immunogenicity of an oral tablet norovirus vaccine, a phase I randomized, placebo-controlled trial

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BACKGROUND. Noroviruses are the leading cause of epidemic acute gastroenteritis and foodborne diarrheal disease in humans. However, there are no approved vaccines for noroviruses. Potential correlates of protection identified through human challenge studies include mucosal IgA, memory B cells, and serum-blocking antibody titers (BT50).

METHODS. We conducted a single-site, randomized, double-blind, placebo-controlled clinical trial of an oral norovirus vaccine to determine safety and immunogenicity. This tablet vaccine is comprised of a nonreplicating adenovirus-based vector expressing the *VP1* gene from the GI.1 norovirus strain and a double-stranded RNA adjuvant. Sixty-six adult subjects meeting inclusion/exclusion criteria were randomized 2:1 to receive a single vaccine dose or placebo, respectively. Immunogenicity was primarily assessed by serum BT50. Additional outcomes included serum ELISA titers, fecal and saliva antibody titers, memory and antibody-secreting cell (ASC) frequency, and B cell phenotyping.

RESULTS. The vaccine was well-tolerated, with no dose-limiting toxicities. Adverse events were mild or moderate. The primary immunological endpoint (increase in BT50 titers) was met in the high-dose group ($P = 0.0003$), with 78% showing a ≥2-fold rise in titers after a single immunization. Vaccine recipients also developed mucosally primed VP1-specific circulating ASCs, IgA$^+$ memory B cells expressing gut-homing receptor ($\alpha4\beta7$), and fecal IgA, indicating substantial and local responses potentially relevant to prevent norovirus infection.

CONCLUSION. This oral norovirus vaccine was well-tolerated and generated substantial immune responses, including systemic and mucosal antibodies as well as memory IgA/IgG. These results are a major step forward for the development of a safe and immunogenic oral norovirus vaccine.

TRIAL REGISTRATION. ClinicalTrials.gov NCT02868073.

FUNDING. Vaxart.

Role of funding source: The sponsor of the study (Vaxart) designed the protocol and had overall responsibility for its conduct. All authors vouch for the accuracy and completeness of the data. L. Kim, D. Liebowitz, and S.N. Tucker had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Conflict of interest: L. Kim, K. Lin, K. Kasparek, K. Gottlieb, D. Liebowitz, G. Trager, S.J. Garg, and S.N. Tucker are employees of Vaxart and have received stock options and compensation as part of their employment.

Submitted: March 15, 2018
Accepted: May 25, 2018
Published: July 12, 2018

Reference information:
JCI Insight. 2018;3(13):e121077.
https://doi.org/10.1172/jci.insight.121077.

Introduction

Noroviruses are the leading cause of epidemics of acute gastroenteritis and foodborne disease worldwide (1, 2). Infection is classically characterized by severe vomiting, diarrhea, and abdominal cramping for 28–60 hours within 10–51 hours of exposure (3). The virus is transmitted by the fecal/oral route, and because of the durability of the virus particles on exposed surfaces (4), severe outbreaks can occur in tight, close-quartered conditions, such as hospitals, military barracks, schools, camps, and ships (5–7).

There are currently no licensed vaccines for norovirus, and lack of an adequate animal model to test efficacy has hindered vaccine development. The most advanced vaccine candidates to date have relied on cell culture–based expression of norovirus VP1, which spontaneously forms a virus-like particle (VLP) that can be subsequently purified. Purified VLPs have been given orally, intranasally, and intramuscularly to mice and humans, usually with adjuvants that improve immunogenicity (reviewed by Riddle et al.) (8). Vaccine approaches in humans have focused on the main disease-causing genogroups of norovirus, GI