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Review

Treatment of norovirus infections: Moving antivirals from the bench to the bedside

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ABSTRACT

Noroviruses (NV) are the most common cause of acute gastrointestinal illness in the United States and worldwide. The development of specific antiviral countermeasures has lagged behind that of other viral pathogens, primarily because norovirus disease has been perceived as brief and self-limiting and robust assays suitable for drug discovery have been lacking. The increasing recognition that NV illness can be life-threatening, especially in immunocompromised patients who often require prolonged hospitalization and intensive supportive care, has stimulated new research to develop an effective antiviral therapy. Here, we propose a path forward for evaluating drug therapy in norovirus-infected immunocompromised individuals, a population at high risk for serious and prolonged illness. The clinical and laboratory features of norovirus illness in immunocompromised patients are reviewed, and potential markers of drug efficacy are defined. We discuss the potential design of clinical trials in these patients and how an antiviral therapy that proves effective in immunocompromised patients might also be used in the setting of acute outbreaks, especially in confined settings such as nursing homes, to block the spread of infection and reduce the severity of illness. We conclude by reviewing the current status of approved and experimental compounds that might be evaluated in a hospital setting.

Contents

1. Introduction . . . 81
2. The clinical challenge of norovirus infection . . . 81
   2.1. Impact of the disease . . . 81
   2.2. The focus on drug development to combat NV . . . 82
3. Therapeutic drug trials in immunocompromised subjects with norovirus infection . . . 82
   3.1. Study of immunocompromised populations with acute norovirus enteritis . . . 82
      3.1.1. Considerations for subject enrollment . . . 82
      3.1.2. Considerations for trial design . . . 83
      3.1.3. Considerations for patient management during trials . . . 83
      3.1.4. Assessment of drug efficacy . . . 83
   3.2. Study of immunocompromised populations with chronic norovirus enteritis . . . 85
   3.3. Study of uninfected immunocompromised populations in a high-risk setting . . . 85
      3.3.1. Considerations in subject enrollment . . . 85
      3.3.2. Considerations for trial design . . . 85
      3.3.3. Clinical monitoring and assessment of drug efficacy . . . 85
   3.4. Extending anti-NV therapeutic trials to other populations at risk . . . 85
4. Current state of anti-norovirus drug discovery . . . 85
   4.1. Drugs and investigational compounds previously administered to humans . . . 87
   4.2. Other nucleosides . . . 87

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4.3. Non-nucleoside RdRp inhibitors . . . 88
4.4. Protease inhibitors . . . 88
4.5. Entry inhibitors . . . 88
4.6. Other compounds . . . 88
5. Summary . . . 88
References . . . 89

1. Introduction

Noroviruses (NV) are notorious for causing epidemics of acute gastrointestinal illness in settings such as schools, cruise ships, nursing homes, and communities. Less widely recognized, however, is the severe burden of chronic NV infection in immunocompromised patients, particularly solid organ and stem-cell transplant recipients, who may suffer prolonged, debilitating diarrheal disease that requires careful fluid replacement and intensive supportive care (Kaufman et al., 2005; Bok and Green, 2012). Detailed understanding of the pathobiology of NV infection and discovery of human anti-NV drugs have been complicated by the absence of a permissive cell culture system for NV or an authentic animal disease model for these important positive-strand RNA viruses, handicaps that have been overcome for other viral infections such as hepatitis C virus. Thus, cellular targets of NV in the intestinal mucosa remain incompletely defined (Bok et al., 2011; Taube et al., 2013), and no antiviral therapies are currently licensed, either to slow the spread of NV outbreaks in healthy populations or to prevent or treat infections in immunodeficient persons. Furthermore, no formal clinical anti-NV drug trials are currently in progress.

Despite the numerous impediments to NV research, important advances have been achieved. Susceptibility to NV infection has been linked to host expression of histo-blood group antigens (HBGA) on the intestinal epithelium that serve as factors involved with NV attachment. Individuals expressing HGBA are designated secretor-positive and susceptible to a wide range of strains; those not expressing HGBA, *i.e.* who are secretor-negative, may be markedly less susceptible to infection (Tan and Jiang, 2007; Jin et al., 2013). Various components of the adaptive immune system including antibodies, CD-4 lymphocytes, and CD-8 lymphocytes contribute to disease recovery and virus elimination (Fang et al., 2013; Tomov et al., 2013). Resistance to NV re-infection is apparently variable and strain-dependent (Zhu et al., 2013). The contribution of specific antibody to protection appears to be based in part on binding to the NV capsid at sites of attachment to HBGA (Higo-Moriguchi et al., in press; Chen et al., 2013). Recent discoveries such as these justify optimism that specific therapeutic countermeasures to NV can be developed in the near future (Rohayem et al., 2010).

Here, we describe acute and chronic NV infection in immunocompromised patients, focusing specifically on organ transplant recipients who have an urgent need for antiviral therapy. We propose options for the potential design of clinical trials in this cohort and outline the clinical and laboratory features of NV illness that might be employed as criteria to evaluate the efficacy of therapy. We follow this discussion by considering how drugs that prove beneficial against chronic infection in immunodeficient patients might also be used to limit the impact of naturally occurring NV epidemics, especially among vulnerable populations such as nursing home or other long-term care facility residents. We conclude by discussing the current status of a number of experimental compounds and drugs that are FDA-approved for other indications or that have shown evidence of anti-NV activity in the laboratory, preclinical investigations, and pilot clinical studies and that might provide promising candidates for testing in a hospital setting.

2. The clinical challenge of norovirus infection

2.1. Impact of the disease

The RNA virus family *Caliciviridae*, of which the genus *Norovirus* is the most consequential member in clinical medicine, was first recognized approximately 40 years ago as a cause of intense, albeit usually self-limited vomiting and/or watery diarrhea (Kapikian et al., 1997; Green, 2013). The recent, marked reduction in the prevalence of rotavirus infection following successful vaccine development, together with the increased availability of sensitive and practical methods for NV detection have established NV as the most common cause of both epidemic and endemic viral enteritis in the US and worldwide (Hall et al., 2011, 2013a). In the US alone, NV is estimated to be responsible for 19–21 million episodes of gastroenteritis and 56,000–71,000 hospitalizations annually, about 570–800 of which are fatal (lifetime risk equal to 1 in 5000–7000) (Gastañaduy et al., 2013; Hall et al., 2011, 2013a; Koo et al., 2013). NV infections are responsible for 1.1 million hospitalizations and 218,000 deaths annually in children in the developing world (Hall et al., 2011, 2013a). In the US, 58% of an estimated annual 9.4 million episodes of food borne illness are caused by NV, making these infections the leading identified causative agent in all age groups of this significant public health problem (Hall et al., 2011, 2013a; Scallan et al., 2011). In a recent survey of 921 hospitals in the US, NV was the most frequent hospital-acquired infection, accounting for 18% of all cases, but more importantly, 65% of all hospital unit closures (Rhinehart et al., 2012).

Nearly two-thirds of all NV outbreaks reported in the US occur in long-term care facilities (Greig and Lee, 2009; Hall et al., 2011, 2013b; Rhinehart et al., 2012). Factors that promote widespread endemic NV infection and epidemic disease, particularly in confined institutional settings, include:

- short incubation time (median 1.2 days) (Lee et al., 2013);
- high virulence and infectivity (Greig and Lee, 2009; Hall et al., 2011; Kroneman et al., 2008; Seitz et al., 2009; Teunis et al., 2008);
- strong resistance to common disinfectants (Park et al., 2010);
- persistence on surfaces and in water (Seitz et al., 2009); and
- fecal shedding of virus, which may last up to 1–2 months in infected persons who have resolved symptoms and are otherwise healthy (Hall et al., 2011, 2013a; Glass et al., 2009; Koo et al., 2013; Milbrath et al., 2013).

Furthermore, the inconsistent and incomplete immune protection that is obtained after a single NV infection, in some circumstances lasting for only up to 30 weeks, maintains susceptibility of all age groups to recurring, acute disease (Hall et al., 2011, 2013a,b; Glass et al., 2009; Koo et al., 2013).

Emphasizing the relationship between immune-competence and control of NV infection, roughly one-third of fatal NV cases occur in the setting of chemotherapy for malignancy or organ transplantation (Trivedi et al., 2013). This number may underestimate the true risk of fatal disease in immunocompromised populations, because until very recently, NV testing for gastrointestinal symptoms was rarely performed in clinical practice (Bok and Green,