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*Evaluation of Nitazoxanide as an Antiviral for Human Norovirus Using Human Intestinal Organoids*

Human noroviruses (HuNoVs) are the leading cause of acute vomiting and diarrhea. In healthy people, symptoms usually resolve within three days; however, in immunocompromised persons, HuNoV infection can become persistent, debilitating, and life-threatening. There are currently no licensed therapeutics for HuNoV due to a near half-century delay in its cultivation. Treatment for chronic HuNoV infection in immunosuppressed patients includes off-label nitazoxanide (NTZ), a broad-spectrum antimicrobial. Nitazoxanide shows antiviral activity in an *in vitro* RNA replicon model of genotype GI.1 HuNoV RNA expression. However, this drug has not been evaluated in infections with commonly circulating HuNoVs. Nontransformed, multicellular human intestinal organoids (HIOs) are a physiologically relevant cell culture system derived from intestinal stem cells that support replication of HuNoV. HIOs have great potential for antiviral studies, as they are permissive for several HuNoV strains and can be generated from different donors, allowing evaluation of the diversity of human responses. Despite these advantages, few studies have used HIOs for antiviral research. A pipeline for NTZ testing was established to inoculate a standard viral dose using 100 half maximal tissue culture infectious doses (TCID0s) and treat cells with 5 ascending drug doses in tandem with cytotoxicity testing. Antiviral activity of NTZ was measured based on viral RNA replication 24-48 hours after infection of HIOs with or without drug treatment. Cell viability was measured to demonstrate that replication inhibition was not due to cytotoxicity across the therapeutic range of the compound. NTZ showed antiviral activity in HIOs; strain-specific responses were observed and mechanisms for these differences are under investigation. HIOs provide a pre-clinical platform to test antivirals against HuNoVs and develop therapeutics to treat norovirus disease.