pitalized children in Vietnam. RV, RSV, and HBoV may increase the severity of ARIs in children.

http://dx.doi.org/10.1016/j.ijid.2014.03.481

Type: Oral Presentation

Final Abstract Number: 14.003
Session: Hot Topics
Date: Thursday, April 3, 2014
Time: 15:45-17:45
Room: Room Roof Terrace

Immunogenicity of monovalent type 1 oral poliovirus vaccine administered at short and standard intervals: A randomized controlled trial, Pakistan, March 2012-May 2013

F. Mir[1,*], F. Quadri[2], O. Mach[3], Z. Bhatti[2], A. Khan[2], R.W. Sutter[3], A. Zaidi[4]

[1] *Aga Khan university, Karachi, Pakistan*
[2] *Aga Khan University, Karachi, Pakistan*
[3] *World Health Organization, Geneva, Switzerland*
[4] *Aga Khan University Hospital, Karachi. Pakistan, Karachi, Pakistan*

Background: Polio eradication is a global health priority and Pakistan is among last three endemic countries. Supplementary immunization activities (SIAs) with oral poliovirus vaccines are usually separated by four week intervals; however, shorter intervals have been used in security compromised areas and for rapid outbreak response. We assessed immunogenicity of monovalent type 1 oral poliovirus vaccines (mOPV1) administered at shorter than usual intervals in a cohort of infants in Karachi, Pakistan.

Methods & Materials: A randomized controlled trial was conducted to compare immunogenicity of two doses of mOPV1 given at 7 or 14 day-intervals with standard 30 day interval. In addition, bivalent OPV1&3 (bOPV) was administered at 30-day interval. Birth trivalent OPV and two study OPV doses were administered and blood samples obtained at birth, six weeks of age and one month after the last OPV dose. Blood was tested for poliovirus neutralizing antibodies.

Results: A total of 1009 newborns were enrolled, and 829 (82%) met eligibility criteria for randomization at 6 weeks; 554 (55%) were included in the per protocol analysis. Seroprevalence of poliovirus neutralizing antibodies for poliovirus type 1 after three doses of OPV was > 95% for all arms. Among those who did not seroconvert after birth dose, no significant differences in seroconversion to poliovirus type 1 after two study OPV doses were found between study arms (75.0% [CI95% = 65-83%] for mOPV1 given at 7 day interval, 75.0% [CI95% = 65-83%] for mOPV1 at 14 day interval, 78.1% [CI95% = 69-86%] for mOPV1 at 30 day interval and 72.6% [CI95% = 63-81%] for bOPV at 30 day interval).

Conclusion: We found no differences in immunogenicity of mOPV1 administered in shorter than standard intervals. These results provide the scientific justification for the expanded use of the short-interval strategy to rapidly increase population immunity, to control outbreaks, prevent importations, and in areas of conflict where limited window of access can be created.

Funding: The World Health Organization

http://dx.doi.org/10.1016/j.ijid.2014.03.482

Type: Oral Presentation

Final Abstract Number: 14.004
Session: Hot Topics
Date: Thursday, April 3, 2014
Time: 15:45-17:45
Room: Room Roof Terrace

Enhancing safety and efficacy of RNAi-based gene therapy for the treatment of chronic hepatitis B

T. Michler[1,*], S. Mockenhaupt[2], S. Grosse[2], D. Grimm[2], U. Protzer[1]

[1] *Institute of Virology of the Technical University Munich, Munich, Germany*
[2] *Heidelberg University Hospital, Heidelberg, Germany*

Background: About 350 million people are chronically infected with Hepatitis B Virus (HBV) and only a fraction will clear the virus during their life-time. Current therapeutic options are unsatisfying, and life-long appliance of nucleoside-analogs can lead to side effects and selection of resistant mutants. A new therapeutic approach is to target viral mRNA transcripts for degradation by the RNA induced silencing complex (RISC). This method holds immense potency since theoretically an effective and long-term suppression of viral transcripts can be achieved by a single dose of a vector encoding for a short-hairpin RNA (shRNA). fter initial enthusiasm, reports of severe side effects in animal studies hampered RNAi-based gene therapies entering the clinics. Several causative mechanisms have been proposed: (1) Oversaturation of endogenous factors, particular of Argonaute 2, leading to breakdown of microRNA processing; (2) off-target effects caused by activity of the passenger strand; and (3) artificial feeding of shRNAs into the microRNA pathway downstream of drosha.

Methods & Materials: We designed a range of recombinant Adeno-associated-virus (AAV) vectors expressing factors to specifically address each of the proposed mechanisms: (1) Co-expression of the shRNA with Argonaute 2; (2) co-expression of the shRNA with a decoy to neutralize the passenger strand; and (3) expression of the same siRNA-sequence from a microRNA backbone using a liver specific polymerase III promoter. Vectors were injected i.v. in HBV-transgenic mice and compared for efficacy of HBV-suppression and signs of toxicity.

Results: While the conventional approach of a polymerase III promoter driven shRNA led to reductions of HBV-parameters of up to 97% but was accompanied by elevated ALT levels and loss of body-mass, co-expression of Argonaute 2 with the shRNA reduced signs of toxicity with similar efficacy of HBV-suppression. More noteworthy, co-expression of the passenger strand decoy with the shRNA not only abrogated toxicity, but also significantly enhanced HBV-suppression with long-term reductions of 99%. Liver specific expression of the microRNA mimic showed ameliorated toxicity but was less efficient in suppressing HBV.

Conclusion: Understanding the mechanisms of RNAi-related toxicity and the rational design of new expression vectors could lead to the development of safe and efficient RNAi-based therapeutics for chronic Hepatitis B.

http://dx.doi.org/10.1016/j.ijid.2014.03.483