1657. Single Dose IV Peramivir Treatment in Pediatric Influenza: Lack of Development of Influenza Virus Variants with Reduced Susceptibility to Peramivir

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Background. Peramivir (PVR) is a potent neuraminidase inhibitor (NAI) with in vitro activity against all influenza virus subtypes. Previous studies demonstrated the efficacy and safety of peramivir as a single dose intravenous (IV) treatment for acute uncomplicated influenza in adults.

Methods. A phase 3 study compared age-appropriate single dose IV PVR to 5 days of oral oseltamivir (OSE) (4:1 randomization, stratified by age) in pediatric subjects age 6-17 years within 48 hours of acute uncomplicated influenza symptom onset. Influenza infection and subtype was confirmed by PCR. In vitro susceptibility of cultured virus to PVR, OSE and zanamivir (ZVR) from paired baseline/post-treatment clinical samples was performed with a MUNANA assay. Sequence analysis of NA and hemagglutinin (HA) genes was performed from uncultured virus. In vitro susceptibility of cultured virus to PVR, OSE and zanamivir from paired baseline/post-treatment clinical samples was performed with a MUNANA assay. Sequence analysis of NA and hemagglutinin (HA) genes was performed from uncultured virus.

Results. 122 subjects were enrolled up to a cutoff date of March 31, 2017 (<2 yrs, n = 72; 2-<7yrs, n = 37; 7-<13 yrs, n = 48; 13-17 yrs, n = 30). Data is shown on 108 subjects randomized prior to the 2016-17 season, of which 101 (94%) received study drug. Full data will be reported.

Influenza was confirmed in 75 (74%) subjects who received study drug: A/H1N1, n = 31 (41%); B, n = 27 (36%); A/H1N2, n = 15 (20%); A/indeterminate and A/H1N1/B co-infected, 1 each. Baseline IC50s for each subtype are summarized:

| IC50 (nM) | PVR | OSE | ZVR |
|----------|-----|-----|-----|
| A/H1N1   | 0.20 (0.05) | 0.61 (0.21) | 0.41 (0.15) |
| A/H1N2   | 0.25 (0.06) | 0.61 (0.16) | 0.51 (0.11) |
| B        | 1.97 (0.64) | 32.77 (13.00) | 2.99 (0.89) |

Two treatment-emergent substitutions were detected in NA or HA genes of PVR-treated subjects: a NA S67A (reversion to wild type) in an influenza B virus and a HA V496V/F mixture in an A/H1N1 virus. Neither substitution was associated with a resistant phenotype. Among PVR treated subjects, no changes were observed in the last positive post-baseline sample PVR median IC50 compared with baseline and no individual subject treated with PVR had an IC50 fold-change from baseline greater than 1.63.

Conclusion. Peramivir had the greatest potency of 3 NAIs tested for all baseline virus subtypes in the order: PVR < ZVR < OSE. Treatment with a single dose of IV PVR was not associated with development of resistance to the drug in this pediatric population.

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1658. 2016–2017 Seasonal Influenza Vaccine Availability at Urgent Care Centers in the state of Arizona, USA

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Session: 173. Viral Treatment and Prevention

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Background. Urgent Care Centers (UCCs) routinely treat episodic conditions requiring immediate but not emergent attention. They offer health care on a walk-in basis in urbanized and convenient locations, with extended business hours. Nationwide statistics estimated more than 7,000 operating UCCs throughout the United States in 2016.

Methods. Utilizing public information, we gathered a list of all operating UCCs in the state of Arizona. Following IRB approval, we conducted a cross-sectional phone survey from January 25th to February 13th, 2017. We assessed whether the 2016–2017 seasonal influenza vaccination was offered at 155/193 (80.3%) of UCCs in Arizona. None of the 6 pediatric-only UCCs provided the vaccine. Among facilities that offered influenza vaccination, 201/155 (12.9%) only vaccinated adults at least 18 years of age, 13 (8.4%) vaccinated adults and children 2-17 years old, 47 (30.3%) vaccinated adults and children 4 years and older, and 57 (36.8%) vaccinated adults and children 6-months or older (Table 1). During the survey period, influenza vaccination was out of stock in 46/155 (29.7%) facilities; with 28/46 (60.9%) of those facilities having no plans to re-order more. Only 9/155 (6.2%) UCCs billed medical insurance to cover the cost of influenza vaccination. Out-of-pocket costs per a single vaccine ranged from $20-80 USD (mean 26.10 USD).

Results. A total of 193/217 (88.9%) facilities met our inclusion criteria to be deemed an operating UCC. The 2016–2017 seasonal influenza vaccination was offered at 155/193 (80.3%) of UCCs in Arizona. None of the 6 pediatric-only UCCs provided the vaccine. Among facilities that offered influenza vaccination, 201/155 (12.9%) only vaccinated adults at least 18 years of age, 13 (8.4%) vaccinated adults and children 2-17 years old, 47 (30.3%) vaccinated adults and children 4 years and older, and 57 (36.8%) vaccinated adults and children 6-months or older (Table 1). During the survey period, influenza vaccination was out of stock in 46/155 (29.7%) facilities; with 28/46 (60.9%) of those facilities having no plans to re-order more. Only 9/155 (6.2%) UCCs billed medical insurance to cover the cost of influenza vaccination. Out-of-pocket costs per a single vaccine ranged from $20-80 USD (mean 26.10 USD).

Conclusion. To our knowledge, this is the first study to assess whether the seasonal influenza vaccine is being administered at UCCs. Our results indicated major inconsistencies among UCCs in Arizona to offer influenza vaccination to the populations they serve, particularly children. Urgent care medicine is now playing an important role in our evolving and expanding health care system, with many people relying on UCCs for their primary health care needs. Efforts are needed to implement strategies to improve influenza vaccination across all ages in this sector. Further studies are warranted to assess seasonal influenza vaccination practices among UCCs nationwide.

Table 1. Minimum age UCC(s) in Arizona would administer the 2016-2017 seasonal vaccine.

| Age (years) | UCC(s) |
|-------------|--------|
| 2           | 1.3%   |
| 2-<7yrs     | 2.6%   |
| 7-<13yrs    | 8.4%   |
| 13-17yrs    | 12.9%  |
| 12-17yrs    | 30.3%  |
| 12-50yrs    | 36.8%  |
| >50yrs      | 1.9%   |

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1659. Intranasal Administration of Integrase Defective Lentiviral Vectors Expressing mAbs Protects from H5 Influenza Virus Challenge In Vivo

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Background. Despite medical advances, we are often unable to rapidly protect non-immune populations from infectious agents. Passive immunotherapy is a fast method of protection, but large-scale administration of monoclonal antibodies (mAbs) in unpractical. The delivery of mAbs using a viral vector can be an attractive alternative to direct mAbs injection. Integrase-defective lentiviral vectors (IDLV) have several advantages including the absence of pre-existing anti-vector immunity and the safety features of non-integration and non-replication. IDLV are maintained in non-dividing cells, and can express steady levels of functional proteins in vivo. We engineered IDLV to express mAbs against the influenza A virus (IAV) hemagglutinin, and tested their ability to protect from IAV in vivo.
Methods. IDLV were produced by co-transfection of transfer, packaging, and envelope plasmids in 293T cells and purifi- cation on sucrose gradients. IDLV were normalized using a colorimetric reverse transcriptase assay. Plasmid expressing mAb VN04-2 was provided by B. Hanson. mAb in the supernatant of transduced cells were detected by western blot and quantified by the Easy-Titer Human IgG Assay Kit. For in vivo studies, 6–8 weeks old mice were infected IDLV either by intranasal (in) or intramuscular (im) route. mAb production was detected by western blot and ELISA. Mice were challenged using the recombinant IAV VN5H51-PR8/CDC-RG derived from IAV A/Vietnam/1203/2004.

Results. We engineered IDLV producing the humanized mAb VN04-2 (IDLV-VN4-2), which is broadly neutralizing against H5 IAV. We found that after transduction of 293T cell with different dosages IDLV-VN4-2, the production of mAb was time and dose dependent. mAb were also functional, and bind specifically H5 HA but not other IAV proteins. We also measured VN04-2 production in the serum of mice, 3, 6, 9, 14, 21 and 30 days after in or im administration of IDLV-VN4-2. We found that levels of mAb were sustained. In separate experiments 5/5 mice receiving IDLV-VN4-2 by the in route and 2/5 mice receiving it by the im route were protected from lethal IAV challenge.

Conclusion. Our data suggest that IDLV may represent an attractive candidate for vector-mediated immunization against infectious disease.

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1660. Antiviral Activity of Peptide Nucleic Acid against Human Parechovirus Type 3

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Session: 173. Viral Treatment and Prevention

Background. Human parechovirus (HPeV) type 3 (HPeV3) is an emerging pathogen in neonatal intensive care units. In neonatal and young infants, specific treatment for HPeV3 infection is currently unavailable. The application of anti-sense technology, such as peptide nucleic acids (PNAs), to viral infection has opened a new era of therapeutics. The aim of this study is to develop PNAs inhibiting HPeV3 gene expression as an in vitro model.

Methods. We designed four PNAs that target domains I, J (base and head of domain I structure), and K of an internal ribosomal entry site (IRES) region within the 5′ untranslated region of HPeV3. The IRES region is needed for the cap-independent translation. The PNAs were conjugated with a penetrating peptide (LIR) and/or XB (R = L-arginine, X = 6-aminohexanoic acid, B = β-alanine), LLC-MK2 cells were treated with 0.1–10µM of each PNA or water-containing growth medium for 4h. The transfected cells were then infected with HPeV3 at the multiplicity of infection (MOI) of 10 for 1h. The infected cells were incubated for 7 days at 37ºC in 5% CO2. Extracellular levels of HPeV3 RNA were measured by real-time PCR on days 0 and 7.

Results. Without any treatment, an extracellular level of HPeV3 RNA increased to 8.2 × 105 copies/µL on day 7. When the cells were treated with 10µM of PNA targeting the domain I of IRES, an extracellular level of HPeV3 RNA was suppressed to 4.7 × 103 copies/µL (−99%) on day 7. Using the same PNA with lower concentra-
tions, 1 µM and 0.1 µM of the PNA suppressed 24% and 0% of extracellular levels of HPeV3 RNA, respectively, which demonstrated the effect is dose-dependent. In contrast, 10µM of PNAs targeting domain J (base, J (head), and K suppressed 94%, 92%, and 32% respectively, in extracellular levels of HPAV RNA, respectively, compared with control.

Conclusion. The PNA (RRX) XB targeting domain I of IRES suppressed extracellular levels of HPeV3 RNA in an in vitro model in a dose-dependent manner. Thus, PNA treatment may be a therapeutic candidate for HPeV3-infected patients. This novel therapy may target other HPeVs in vitro and in vivo, given that the target sequence used in this study is identical to those of other clinically significant HPeVs.

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1661. Preventing Respiratory Viruses in the Neonatal ICU

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Session: 173. Viral Treatment and Prevention

Background. Infants in the neonatal ICU can acquire respiratory viruses from ill healthcare personnel (HCP), visitors, or other infants. We describe the epidemiology of respiratory viruses and infection prevention and control interventions aimed to reduce acquisition and transmission of respiratory viruses in our NICU.

Methods. From May 2011 to December 2016, we tracked respiratory virus infections detected by a multiplex reverse-transcr iptase (RT)-PCR assay (FilmArray, Biofire, Inc.) in our 58-bed level IV NICU (~1,000 annual admissions). Testing was ordered for clinicians treating for symptomatic infants. Infants with positive RT-PCR tests generally remained on contact/droplet precautions throughout their NICU stay. ICP were asked to complete a sick and report to Workforce Health and Safety if they became ill at work. Ill visitors were not permitted in the NICU, as enforced by written educational materials and signage, but formal screening was not performed. Starting in January 2015, asymptomatic infants exposed to RT-PCR-positive index cases were screened by RT-PCR, on put contact/droplet precautions for the incubation period (IP) of the index case’s virus, and screened again at IP end. Starting in December 2015, infants exposed to another infant’s index case. We assessed respiratory illness events (≥2 infants), clusters (≥3 infants), and outbreaks (≥3 infants); all were defined as detecting geographically related cases within the relevant IP. We determined screened infants who had positive RT-PCR tests.

Results. During the 5-month observation period, 79 infants had 83 viruses detected (~1.8% of admissions). Rhinovirus (EV/RE) were most common (n = 59) and caused 1 outbreak of 7 infants, 4 clusters, and 5 dyad transmissions. Adenovirus caused 1 breakout of 5 infants. Two dyad transmissions occurred for parainfluenza. Apocaudic cases of RSV (n = 5), coronavirus (n = 2), and influenza (n = 2) occurred. Ill household contacts were identified for 10 infants. No HCPs were identified with respiratory illnesses. Since January 2015, 8 screened infants had positive RT-PCR tests. Since December 2015, only 1 transmission dyad (RV/RE) occurred.

Conclusion. Preliminary data suggest that our interventions have reduced the burden of respiratory viruses in the NICU.

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1662. Use of Oral Ribavirin for the Treatment of RSV Infections in Hematopoietic Cell Transplant (HCT) Recipients

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Session: 173. Viral Treatment and Prevention

Background. The benefit of aerosolized ribavirin (AR) in reducing the risk of progression of RSV infections and RSV-associated mortality in HCT recipients has been recognized, yet there is a paucity of data assessing the use of oral ribavirin (OR) in this patient population. We evaluated outcomes associated with the use of OR compared with AR in HCT recipients.

Methods. Retrospective review of all HCT recipients with RSV infection treated with OR or AR during three RSV seasons (September 2014 – February 2017). An established immunodeficiency Scoring Index (ISI) was applied to identify patients at high risk for progression and death based on host risk factors. Mortality, progression to lower respiratory infection (LRI), and need for ICU admission was compared among recipients of AR and OR.

Results. A total of 107 patients were treated with OR (n = 42, 39%) or AR (n = 65, 61%). Recipients of AR and OR were equally likely to be high-risk by ISI scoring (11% vs. 10%, P = 1.00). Fifty-three patients (50%) presented with upper respiratory infection (URI) of whom 15 (25%) progressed to LRI. There was no difference in the rate of URI progression to LRI between patients who received AR (23% vs. 18%, P = 0.53). No difference was found in 30-day mortality rates based on treatment strategy (8% vs. 5% OR, P = 0.70). Interestingly, 90-day mortality was found to be significantly lower among patients who received OR vs. AR (20% vs. 5%, P = 0.04). No significant difference in rates of ICU admission and requirement for mechanical ventilation were found between the two groups. For the 99 inpatients at time of diagnosis, median (interquartile range) length of stay was 7 (5 – 19) days, and was similar for patients on either treatment modality. Eight patients were treated for RSV on an outpatient basis and all received OR.

Conclusion. HCT patients with RSV had similar outcomes when treated with AR and OR, OR may be a safe and effective alternative to AR for prevention and treatment of RSV in HCT patients with significantly reduced cost.

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1829. Pharmacokinetics (PK) of Eravacycline in Subjects with Renal or Hepatic Impairment Compared with Healthy Subjects

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Session: 231. Clinical Study with New Antibiotics and Antifungals

Background. Eravacycline (ERV) is a fluorocycline being developed for the treatment of serious infections, including those caused by multidrug-resistant pathogens. The PK of ERV in subjects with end stage renal disease (ESRD) or hepatic impairment (HI) were investigated.