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1050. Phase 3 trial to evaluate the Safety, Tolerability, and Immunogenicity of V114 Followed by 23-valent Pneumococcal Polysaccharide Vaccine 6 Months Later in At-risk Adults Aged 18–49 Years (PNEU-DAY): A Subgroup Analysis by Baseline Risk Factors

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Session: P-60. New Vaccines

Background. Risk factors (RFs) for pneumococcal disease (PD) in immunocompetent adults contain lifestyle habits, behavioral, or living in a community with increased risk of PD transmission. RF stacking of comorbidities is associated with a higher incidence of PD, approaching that of immunocompromised individuals. Pneumococcal vaccination of certain adults is recommended with the 23-valent pneumococcal polysaccharide vaccine (PPSV23) alone/sequentially with pneumococcal conjugate vaccine (PCV). V114, an investigational 15-valent PCV, contains 2 epidemiologically important serotypes (STs), 22F and 33F, in addition to the 13 STs in 13-valent PCV (PCV13).

Methods. PNEU-DAY was a Phase 3 study evaluating V114 or PCV13 administered on Day 1, and PPSV23 given 6 months later, in adults aged 18–49 years with or without RFs. This subgroup analysis assessed safety, tolerability, and immunogenicity of V114 and PCV13 based on the number of baseline PD RFs, which included chronic lung, heart, and heart disease, diabetes mellitus, tobacco use, and alcohol consumption. Adverse events (AEs; overall and solicited) were collected after each vaccination. Immunogenicity assessment was based on ST-specific opsonophagocytic activity (OPA) at 30 days after each vaccination. Subgroup analyses were conducted by RF group (0, 1, or 2 RFs for PD).

Results. Among the 1515 participants randomized to V114 (n=1135) or PCV13 (n=380), 25.2% had no RFs, 54.7% had 1 RF and 20.1% had ≥2 RFs for PD at baseline. The proportions of participants with solicited AEs following V114/PCV13 and PPSV23 were comparable across the 3 subgroups, with injection-site pain, malaise, and fatigue being the most common. V114 and PCV13 were immunogenic in all subgroups based on OPA geometric mean titers (GMTs) at 30 days post-vaccination for the 13 shared STs (Figure); in addition, V114 induced a robust immune response to the 2 unique STs (22F, 33F) in all subgroups. PPSV23 following PCV13 was immunogenic for STs contained in V114 according to Figure.

Figure. Serotype-specific OPA GMTs at baseline and 30 days post-vaccination with V114 and PCV13 by number of baseline risk factors (per-protocol population)

Conclusion. Among successfully treated PLWH, we observed low magnitude post-dose HIV blips that were not more common in vaccine vs. placebo recipients and did not result in loss of virologic suppression. This data is favorable for the deployment of the EVD vaccines in this trial in areas of high HIV endemicity.
1051. Characterization of Immune Responses to a Live-Attenuated Tetravalent Dengue Vaccine

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DEN-203, 204 and 205 study groups

Session: P-60. New Vaccines

Background. A safe and effective vaccine against dengue is needed to address an unmet medical need that affects a large portion of the world's population. Takeda's live attenuated tetravalent dengue vaccine candidate (TAK-003) has shown protection in an ongoing Phase 3 efficacy trial. TAK-003 contains an attenuated dengue type 2 virus (DENV-2), and 3 genetically modified viruses in which the structural proteins from each of the serotypes 1, 3 and 4 have been placed into the DENV-2 backbone. TAK-003 was shown to be effective at treating CDI and decreasing subsequent recurrence compared to vancomycin. However, the precise mechanism of action of riluzolide has yet to be fully elucidated. In this study, riluzolide clearly co-localises with DNA in C. difficile and binds with high affinity to the minor groove of DNA. These interactions are predicted to have consequences on cellular functions within C. difficile.

Methods. High resolution confocal microscopy was used to track the intracellular localisation of riluzolide in C. difficile. Fluorescence intensity was used to characterise the DNA binding properties of riluzolide; sequence specificity was demonstrated with AT- or GC-rich DNA polymers, and tight binding was shown using short double-stranded oligonucleotides. Hanging drop vapour diffusion enabled co-crystalisation and subsequent structural determination of DNA-bound riluzolide.

Results. Confocal microscopy revealed clear co-localisation of riluzolide to the DNA within C. difficile. Riluzolide demonstrated a dose-dependent increase in fluorochrome in response to increasing concentration of target DNA. Fluorescence binding studies revealed that riluzolide shows a preference towards AT-rich DNA sequences. Tight binding characteristics were demonstrated by riluzolide in complex with short double-stranded oligonucleotides, returning dissociation constants (K) of 20 – 50 nM. Crystalisation enabled co-structures of riluzolide bound to the minor groove of double-stranded DNA oligonucleotides to be observed.

Conclusion. Riluzolide demonstrates tight binding with sequence specificity within the minor groove of DNA and co-localises with DNA in C. difficile. Further analysis is ongoing to fully understand this novel mechanism of action, the downstream consequences of these interactions and how they contribute to the bacterial activity of riluzolide.

Disclosures. Clive Mason, PhD, Summit Therapeutics (Employee, Shareholder) Tim Avis, n/a, Summit Therapeutics (Shareholder) Christie Coward, PhD, Summit Therapeutics (Employee, Scientific Research Study Investigator, Shareholder) David Dowd, PhD, Summit Therapeutics (Employee, Scientific Research Study Investigator, Research Grant or Support)

Session: P-61. Novel Agents

Background. The β-Lactam Inhibitor QPX7728 Restores the Activity of β-Lactam Agents Against Contemporary Extended-Spectrum β-Lactamase (ESBL)-Producing and Carbapenem-Resistant Enterobacteriaceae (CRE) Isolates, Including Isolates harbouring Metallo-β-lactamase (MBL) genes

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