U.S. FOOD & DRUG ADMINISTRATION

Wrap Up: Day 1

Session 1: Chronic hypertension

- Most drug development for treatment of hypertension are conducted in adults first
  - FDA can require pediatric development under certain circumstances
  - Cannot use retroactively for drugs already approved
  - FDA can incentivize studies
- 61 drugs approved in adults; on 16 drugs approved in children
  - ACEI; ARB; only 1 CCB and 1 beta blocker!
  - 9/16 approved 6 years of age and older
  - 3/16 approved < 6 years of age: enalapril (1 month of age), candesartan and valsartan (1 year of age)
  - 4/16 “approved”; have dosing information for children : hydralazine; chlorothiazide and hydrochlorothiazide; minoxidil approved 1979

Session 1: Chronic hypertension

- Current state of antihypertension development
- New dosage forms—FDA can require studies under PREA
- Here is the opportunity: when and how do we collect information to fill gaps in approvals (e.g., < 6 years of age)
  - What studies are needed?
  - What studies are feasible?
- How can pediatric extrapolation be used?
- What off-label use can be leveraged?
- What study designs can be considered?

Similarities and Differences between adult and pediatric chronic hypertension

- Similar pathophysiology
- Similar biology
- Target organ damage is the same
  - Physiology is similar; alterations in pulse wave velocity; CV disease; kidney disease; retinopathy; stroke and dementia
- Measurement is the same
- BP norms are different: static vs. age/percentile-based thresholds
- Comorbidities less common in children more common in adults
- Etiologies are different: primary hypertension more common > 6 years of age; less common < 6 years of age
- Treatment paradigms different
  - adults generally use common dose and escalation; emphasis on combination therapy
  - Pediatric: lack of data on combination therapy
- Fewer patients
- HTN trials have relied on validated surrogate (BP): SBP in adult trials but DPB in some pediatric trials

Similarities and Differences between adult and pediatric chronic hypertension

- Endpoint measurement in clinical trials
  - SBP reduction compared to placebo based on office BP or use of ABPM
  - Achievement of target BP (responder analysis)
- Efficacy seen in all classes studied
- Anti-hypertensives lower BP in all age groups
  - RAAS blockers may have greater response given greater incidence of secondary HTN
- Older HTN drugs lack good dosing information

Off-label Prescribing Practices and Medication Errors

- Off label prescribing common for pediatric HTN
- Outpatient HTN medication usage study: 70% were off-label
- Neonatal hypertension: 100% off label
- Clearly are gaps between needs and guidelines and FDA labeling
- Liquid preparations
  - Issues with palatability (taste, smell, volume)
  - Issues with shelf life; administration
  - Osmolarity issues with small infants
- Newer dosage forms
  - Minitabs/pellets: no taste, no refrigeration
  - Neonates can take minitab down to 2mm minitab
- Appropriate dosage forms are not always available
- When appropriate formulation not available
  - Crush/mix: appropriate food to mix with
  - Compounding pharmacies not always available
  - Access issues
- Compounding errors can occur always occur when there is a need to manipulate the product

Age-appropriate Pediatric Formulations

- Needs: Can a child take it and Will a child take it?
  - Flexible and accurate dose methods of administration
  - Stability
  - Safety of excipients both based on type and amount
  - Acceptability
    - Palatability (taste, texture, smell)
    - Swallowability (size, shape, texture)
    - Administration
- Challenges
  - Low volume products
  - Requires manufacturing equipment and validation
  - Supply chain
  - In-process controls and equipment checks for accurate dosing capabilities; content uniformity

Panel 1

- What are the most significant unmet needs in the pharmacological management of hypertension in pediatric patients?
  - Approved treatments for patients < 6 years of age
  - More treatment options for older age children and adolescents with primary hypertension and metabolic syndrome
  - New agents and fixed dose-combinations for HTN and treatments for uncontrolled hypertension
  - Agents with longer acting medications and drugs that do not have drug interactions
  - Dosage forms that are suitable for all age groups particularly in neonates
  - Surrogate marker endpoints (comparative efficacy)
  - Excipients that are safe especially in neonates
  - Assessment of safety of excipients

Panel 1

- What are differences between pediatric-onset and adult-onset hypertension?
  - Differences between etiologies between < 6 year-olds and > 6 year-olds so RAAS blockade seen to be useful but treatment of HTN could include both HTN regardless of etiology
  - Response to treatment will depend on etiology
  - Is there an expectation that anti-hypertensive drugs would not work
  - Measurement issues exist but can be addressed
  - Diastolic BP elevations higher in CKD and secondary HTN
  - Systolic BP elevations higher in primary hypertension
  - Endpoint in adult trials are different than endpoints in pediatric trial
  - Differences in PD response between pediatric and adult hypertension
- Would any of these differences preclude inclusion of these patients in a pediatric HTN trial?
  - No

Panel 1

- Is the pharmacologic response to antihypertensive drug classes broadly expected to be similar across adult and pediatric patients?
  - Expected response should be similar between adults and adolescents
  - Neonates: are they different?
- Are there differences in drug responses within the pediatric age spectrum and what biological/developmental factors are most likely to drive those differences?
  - RAAS is more involved in secondary hypertension, particularly CKD
  - Safety/Toxicities should also be considered
- Would any of these differences preclude inclusion of these patients in a pediatric HTN trial?
  - No

Dose Response and Exposure Response Relationships for ARBs and Safety

- Candesartan
  - Exposure response and dose-response relationships between older and younger patients are similar
- Valsartan
  - Slightly lower response but there is overlap between older and younger children is similar
- Supports the acceptability of extrapolation of efficacy from older pediatric patients to younger patients for ARBs
  - Must consider similarity of disease
  - Must consider safety
- Safety Considerations
  - Different classes of drugs carry different potential risks
  - Age dependent risks based on maturation and development of glomerular and tubular function
  - Underlying disease and comorbidities affect risk

Panel 2

- Lessons learned and recommendations
  - Use weight-based dosing
  - Similarities in endpoint measurement in pediatric studies, particularly in younger population
  - Consider pooling of placebo patients across studies
  - Acceptability of placebo arm in trials
  - Reluctance of families to enroll in studies if safety is not clear
  - Optimizing communication and involving patients in trial design
  - Long-term extension
    - How long is long enough? 4-month study for durability of lowering of BP effect
    - Consider burden to family
    - Based on safety questions that need to be answered; e.g. longer-term for growth/development; cardiac sequelae

Modelling and Simulation and Dose Prediction

- Dose selection is challenging particularly for patients < 6 years of age
  - Iterative process based on accumulating data in adults and then children
  - Develop PBPK and/or popPK model
  - Collect pediatric data and then optimize model for younger pediatric patients
- Developmental changes that affect dosing
  - Metabolizing enzymes CYP system; UGT
  - Renal function; hepatic transporters; renal transporters
  - Modelling of mAbs also have special considerations
- Blood sampling scheme should take into account the acceptable limits

Innovative Trial Designs and Leveraging Existing Data

- Newer designs available
  - Use of novel controls: external control; hybrid; synthetic control
  - Adaptive design
  - Bayesian design
  - Master protocols: basket; umbrella
  - Patient/Family Unit centered study design considerations: incorporate patient and family choice in study designs early

Panel 3

- What are the gaps in knowledge for HTN for the following classes in patients 1-6 years of age
  - ARB/ACEi: Confidence in ARBs < 6 years of age for exposure response; gap for all the other drug classes
  - Similarity in CKD and non-CKD in exposure response
  - No comparative effectiveness studies in children
  - Safety findings including neurocognitive effects and long-term safety and efficacy
  - Combination therapies vs. maximizing single agents
  - Dosing changes as child grows; would PK data help to understand this observation
- BUT, the trials conducted to date demonstrate that the drugs that work in adults also work in controlled pediatric clinical trials
- What studies can be designed to address these gaps in knowledge
  - PK studies in children 1-6 for dosing (can be in children already being treated—prevalent population)
  - Include patients down to 6 years of age in all new anti-HTN drugs
  - Use sources such as PedsNet to collect safety data
  - External control arm could be used
  - What data are needed to evaluate certain specific risks? Clinical trial data would certainly help; communication with families can also help but also to study what matters to families—cognition, absenteeism, appetite
  - Needs to be feasible and generalizable

- What about neonates?

- What other infrastructure must be in place to collect this information to make these studies more feasible?
  - Decentralized trials
  - Involve families in trial design
  - Minimize discomfort
  - Communication with patients from clinicians (nephrology community)

Day 2: Uncontrolled Hypertension

- Drugs are now being developed for uncontrolled hypertension in adults
- FDA has the opportunity to require studies in children based on adult drug development under PREA under certain circumstances
- Is there an unmet need in children?
- If so, what population of children can be defined?
- What types of study designs can be considered?

Uncontrolled and Resistant Hypertension

- Adult
  - Uncontrolled hypertension is clearly a risk factor for stroke, MI, Cardiorenal metabolic syndrome
- Uncontrolled hypertension: BP is greater than goal
- Resistant hypertension: maximally treated with at least 3 drugs, including a diuretic, continued BP greater than goal or BP controlled with 4 or more antihypertensive medications
- Categories of uncontrolled hypertension severity similar to hypertension criteria
- Pediatrics
  - No definitions for uncontrolled or resistant hypertension
- Pathophysiology: multifactorial
  - Socioeconomic factors cannot be ignored
  - Adult: arterial stiffness; ET-1 elevation (e.g., obesity, sleep apnea)
  - Pediatrics: secondary hypertension: RAAS activations (aldosterone excess, RAAS resistance, primary hyperaldosteronism)
- An opportunity to better define uncontrolled hypertension in pediatrics

Treatment of uncontrolled hypertension in adults and pediatrics

- Additional considerations:
- Again, socioeconomic factors
- Nonadherence including the need to take multiple pills
- Comorbid conditions and drug interactions
- Medications available
  - Direct Renin Inhibitors: Aliskirin—(approved for hypertension) not approved in children
  - Aldosterone synthase inhibitors: Lorundrostat; Baxdrostat; not approved for children
  - Endothelin receptor antagonists: ambrisentan; macitentan; not approved for hypertension but approved for PAH; aprocitentan approved for uncontrolled hypertension
  - Angiotensinogen synthesis inhibitor: (small interfering RNA) not approved yet in any population
  - Potential treatments: SGLT2, GLP-1
- Role of combination products: combination products at lower maximum doses can achieve better effect

Panel 3

- Based on the adult programs is there a pediatric population that could benefit from drugs being developed?
  - Could define the population and use as add on therapy; those who need an additional agent
  - Strict definition of treatment resistant may not be absolutely necessary; the basic principle is similar between adults and pediatric patients; that they are not optimally controlled despite therapy
  - Etiology of the hypertension in this situation may not matter but not confident yet
  - Population would include pediatric patients 1-17 years of age
- Study design considerations
  - May not need RCTs for PK/PD and safety—confidence that the approved in adults provide confidence that the drug will likely work in pediatric patients in patients 6-17
  - Could potentially do a similar trial in 1-6 years of age but would be important to carefully evaluate the potential safety particularly in patients < 2 years
  - Need for long-term safety information particularly for agents with a novel mechanism of action. How long?
  - Do we need controlled safety?

Special Thanks

- Colleagues from M-CERSI: James Polli, Dana Hammell, Keiasia Robinson, Heather Mattern
- DPMH: Heather Buck, Michelle Pollack, Meshaun Payne
- Staff from the Office of External Affairs
- Workshop planning committee members

Thank You