Development of Non-Traditional Therapies for Bacterial Infections
Clinical Pharmacology Considerations

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Disclaimer

- The content of this presentation reflects the opinions of the speaker and does not necessarily represent the official position of CDER, the Agency, or the Federal Government

Types of Non-Traditional Antibacterial Therapies

Products that exhibit direct bacterial effect and can be used as monotherapies

Example of targets	Types of drugs
Bacterial cell membrane	Lysins; Lantibiotics; Peptides; Antibody-Antibiotics conjugate
Conventional MIC-based PK/PD targets may be applied for some of these products	

Products that do not have direct bacterial effect but enhance efficacy of SOC antimicrobials in adjunctive therapies

Functions to enhance Abx effect	Examples of targets	Types of drugs
Restore	β-lactamase; Efflux pump	Small molecules; **Biologics & peptides:** • Peptides • Lysins • mAbs • Recombinant proteins
Augment	Virulence factors (e.g., toxins); Immune factors (e.g., CD28)	
Prevent resistance	Gut β-lactams; Efflux pump	
MIC-based PK/PD targets are not relevant for most of these drugs		

SOC: standard of care; Abx: antibiotics; mAbs: monoclonal antibodies

Non-traditional therapies (NTTs) span a variety of products; the presentation will focus on biologics & peptides

Pharmacokinetic (PK) Considerations

- **Differences in PK behaviors were observed in infected patients vs. healthy subjects**
  - Faster clearance and shorter half-life for some mAbs in infected patients
  - Slower clearance and higher exposures for some peptides in infected patients
  - PK differences in subset of patients
- **Immunogenicity is observed in most NTT biologic & peptide drugs**
  - Higher positive anti-drug antibody (ADA) rate for some lysins following systemic administration
  - Monitor immunogenicity across entire drug development program
  - Develop neutralizing antibody assay, if needed
- **Understanding the drug's tissue distribution is important**
  - Multiple barriers may exist for biologic & peptide drugs to distribute to the site of infection

Immunogenicity Guidance for Industry:

Immunogenicity Assessment for Therapeutic Protein Products (2014)

Assay Development and Validation for Immunogenicity Testing of Therapeutic Protein Products (2016)

Pharmacodynamic (PD) Considerations

- **Evaluation of mechanism-based PD biomarkers in infected patients**
  - MIC-based PK/PD approach applies to limited NTTs
  - For some peptides with short half-life (~5 min), assessing the long-lasting PD effect (~72 hr) is critical
  - Examples of mechanism-based PD biomarkers: binding of antibody to antigen (e.g., anti-toxin neutralizing antibody when targeting toxins), opsonophagocytic killing effect when targeting exopolysaccharide on bacterial cell surface
- **Determination of clinically relevant downstream effects in patients**
  - For example, effect of immunomodulators on the level of cytokines
  - Impact of NTTs on the antibacterial effect of SOC antibiotics in adjunctive therapy
- **Assessment of clinical PK/PD relationship to support dose selection**

Dose Selection

- **Dose selection based on pre-clinical PK/PD data may not be sufficient**
  - Pre-clinical PK/PD information is useful for Phase 1/2 dose selection
  - PK/PD results from patients are preferred for Phase 2/3 dose selection
- **Conduct dose ranging studies to facilitate dose selection**
  - Consider evaluating multiple dose levels, and multiple dose ratios in combination therapy
  - Determine mechanism-based and clinically relevant PD effects
- **Perform exposure-response (E-R) analyses to assist dose selection**
  - PK/PD relationship
  - Exposure-efficacy relationship
  - Exposure-safety relationship
  - Drug exposure at the site of infection may be more informative for E-R analyses

Additional Clinical Pharmacology Considerations

Most current NTTs are at the early development stage;
Clinical Pharmacology studies needed for NTTs should be assessed on a case-by-case basis

- **Drug-drug interaction (DDI) studies**
  - Clinical DDI assessments in combination therapies
  - Therapeutic protein DDI for cytokine or cytokine modulators (e.g., immunomodulators)
- **Effect of hepatic or renal impairment on the PK of NTT biologic & peptide drugs**
  - Hepatic impairment usually does not affect PK of mAbs, with some exceptions
  - Renal impairment may alter PK of therapeutic proteins with molecular weight <69 kDa
- **Effect of NTT biologic & peptide drugs on QTc interval**
  - mAbs usually are not associated with clinically meaningful effect on QTc interval
  - Further assessments may be needed for other biologic & peptide drugs
- **Other Clin Pharm studies on a case by case situation**

Challenges

- **Understand the disposition of NTTs in infected patients**
  - Characterize immunogenicity and its impact on PK/PD, safety, and efficacy
  - Determine drug distribution to the infected tissues
    - Problems of accessibility and representation of tissue samples
- **Understand the drug effect of NTTs to select the dose for Phase 3 studies**
  - Identify appropriate PD biomarkers for non-traditional therapies
  - Understand the clinically relevant pharmacological effects of NTTs in affecting the antibacterial activity of concomitant antibiotics
  - Link pre-clinical PK/PD data to humans when lacking human PK/PD data
    - Phase 2 dose selection of most current NTTs under development are based on in vitro or animal PK/PD data


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