Superiority and Organism-Specific Clinical Trials of Anitbacterial Agents

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Disclosures

• In the last 12 months, Dr. Boucher has served as a consultant/advisor to:
  • Basilea, Durata, Merck (adjudication committee), Paratek, and Rib-X
BAD BUGS, NEED DRUGS
The 10 X ’20 Initiative: Pursuing a Global Commitment to Develop 10 New Antibacterial Drugs by 2020

http://www.idsociety.org/10x20
The Stakes Are High
www.AntibioticsNow.org

Rebecca Lohsen (17 yr) -- Dead

Mariana Bridi da Costa (22 yr) -- Dead

Tom Dukes -- 8" of colon resected, colostomy

Bryce Smith (14 mo) -- survived, $1 million hospital bill

Carlos Don (12 yr) -- Dead

Ricky Lannetti (21 yr) -- Dead
IDSA
Meeting Regulatory Challenges - Guidance

• Predictable, feasible guidance needed on
  • Standard antibiotic indications – often the initial development pathway
    • FNIH process
    • Feasibility key – consider the “costs” of various options (e.g., inclusion criteria that limit enrollment)
  • Pathways for new Gram-negative antibiotics (e.g., urinary tract, intra-abdominal infections, and pneumonia)
    • For newly-emerging resistant pathogens these studies can’t easily be done
    • Tiered approach (efpia) and LPAD
To address the “unmet need” gap, IDSA proposed several program designs that could allow approval of new drugs for resistant Gram-negative infections:

- Small, well conducted studies, to enable conditional approval for drugs of critical public health need while placing limitations on the use/promotion of such drugs until follow-up studies are completed.
- Superiority pathways
  - less feasible as new drugs emerge
- Bacteria- or “organism-specific” rather than disease-specific approval
- Pathway must permit development of multiple drugs over time
Recognized need for means to overcome ethical and practical barriers to studying drugs for infections caused by drug-resistant pathogens

- Parenteral drugs for MDR pneumonia, BSI
- Oral drugs for UTI/pyelonephritis

Spellberg et al. CID 2012
Study Design Options

- Heirarchical Noninferiority-superiority Clinical Trials
- Monotherapy Superiority Clinical Trials
  - Less severe infection with possible rescue therapy
    - e.g. Uncomplicated UTI
  - Trials of extreme drug-resistant and pan-drug resistant infections
    - No effective comparator
- Safety endpoints
  - Study of new, potentially less toxic agent

Spellberg et al. CID 2012
Study Design Options (continued)

- Nested superiority-NI trial design
- Combination therapy or “add on” trial design e.g., salvage HIV
- Historical control superiority studies
  - Data less robust
  - Explicitly discussed in ICH E10
    - “well documented population”
    - Limit to “situations in which the effect of treatment is dramatic and the usual course of disease highly predictable.. Objective endpoints”
- May fit many MDR/XDR infections!

Spellberg et al. CID 2012
Challenges in Superiority Studies of Infections Caused by Drug-Resistant Bacteria

Challenges:

- Diagnosis
  - Need for molecular diagnostics is GREAT!
- Need for rescue therapy
- Site selection
  - Need high prevalence of resistant pathogens AND clinical trials expertise
    - Hope: increased networks/NIH resistance group
- Empirical vs targeted enrollment
  - Empirical enrollment – risk: bias
  - Targeted enrollment – risk: effect of prestudy abx

Spellberg et al. CID 2012
Meeting Challenges in Superiority Studies of Infections Caused by Drug-Resistant Bacteria

- Bias in historical control studies
  - Pharmacometric approaches to defining historical control response rates
- Informed consent in critically ill patients
  - Emergency exception
- Patient identification to ensure enrollment
  - Strategies to mitigate:
    - Organism specific enrollment – i.e., allow inclusion of infections at multiple sites caused by the resistant pathogen
    - Smaller development programs
    - Alternative statistical methods (Bayesian design)

Spellberg et al. CID 2012
Organism Specific Superiority Clinical Trials

- Established precedent – invasive fungal infections

- Key design issues:
  - Justify types of diseases to enroll
  - Drug should be known to penetrate relevant tissues
  - Pk in relevant populations should be understood
  - Drug activity in relevant tissues

Spellberg et al. CID 2012
Superiority Clinical Trials
Design Considerations

- **Endpoints**
  - Clinically relevant, objective
  - Should reflect how patient “feels, functions or survives”
  - In life-threatening disease, composite to include mortality
  - Historical control – mortality likely primary

- **Sample size**
  - Flexibility key
  - One phase 3 trial may suffice in certain circumstances
    - Depends on trial design, conduct, objective endpoints, robust results
    - Postmarketing studies likely required

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Superiority Clinical Trials
Design Considerations

- Comparator drugs
  - For MDR/XDR not necessary (and may be unethical) to limit comparators to FDA/EMA-approved drugs
    - Should be driven by the protocol and not left to individual site investigators
  - Goal: select agents with highest probability of demonstrating activity

Spellberg et al. CID 2012
Limited Population Antibacterial Drug (LPAD) Mechanism

At least 15 drug companies as well as multiple medical societies (including AMA) and health orgs now support LPAD

http://www.idsoociety.org/2012_LPAD_Proposal_Backings/
Limited Population Antibacterial Approval Pathway

• IDSA proposed this new regulatory pathway to enable conduct of smaller trials for XDR/PDR pathogens

• President’s Council of Advisors on Science and Technology (PCAST) called for the establishment of a new pathway for initial approval of drugs shown to be safe and effective in a specific subgroup of patients
  • Specifically discusses a Special Medical Use pathway, using obesity and antibiotics to treat multidrug resistant infections as examples
  • This proposal aligns with IDSA’s proposal for a Limited Population Antibacterial Drug (LPAD) approval pathway at the Food and Drug Administration (FDA)

Spellberg et al. CID 2012
Limited Population Antibacterial Drug (LPAD) Mechanism

- LPAD drugs would be studied in substantially smaller, more rapid, and less expensive trials
  - For some antibiotics to treat severe infections caused by the most resistant bacteria, pivotal trial size may be as small as 30 - 100 patients
- Narrow indications
  - LPAD drugs narrowly indicated for a small, specific population of patients for whom the drug benefits outweigh risks
- For patients with serious infections and inadequate current treatments, a greater degree of uncertainty about overall risk associated with a drug can be tolerated
- The drug would not be appropriate for use against non-serious or non-resistant infections

Spellberg et al. CID 2012
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BAD BUGS, NEED DRUGS
The 10 X '20 Initiative: Pursuing a Global Commitment to Develop 10 New Antibacterial Drugs by 2020
Additional Related IDSA Policy Reports/Continued Advocacy

Additional Reports:

- “Bad Bugs, No Drugs; No ESKAPE”; IDSA’s latest update on the antibiotic drug pipeline; Boucher et al, CID, January 1, 2009
- Numerous position papers focused on FDA clinical trial designs (CAP; cSSSI; HAP/VAP, superiority for MDR organisms)
- The 10 x ‘20 Initiative, Global Commitment, April 15, 2010