Issues regarding non-inferiority within the anti-bacterials area

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Topics Covered

- Disease area background
- The need for non-inferiority studies for anti-bacterials
- Explanation of the controversies of using non-inferiority studies in this area
- Work that has been undertaken to
  - Establish the placebo effect
  - Define a non-inferiority margin
- Discuss whether some alternative endpoints could move us away from NI study
- Conclusions

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Disease area background (1)

- Infection is grouped into general and specific infections
  - Eg Complicated skin and skin structure infections, Pneumonia,
- Within the broad categories, infections tend to share common pathogens
- With each grouping there are a number of different pathogens involved
  - eg Community Acquired Pneumonia:
    Streptococcus pneumoniae, Haemophilus influenzae,
    Staphylococcus aureus, etc
- The human therapeutic effect is the result of the drug's ability to kill or inhibit the growth of micro-organisms

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Disease area background (2)

- At the time of treatment you do not know what the specific pathogen is or indeed if it is definitely a bacterial infection
- Technologies to identify pathogens are far from perfect
  - Pathogen identification rates vary but can be <40%
- Main focus in terms of efficacy assessment is on the “Test of cure” visit
  - 7 to 14 days after treatment has stopped, depending on half-life
    - those with a long half life would need a later visit
  - Looking to ensure cured in absence of the drug
  - Cure is defined as: Complete resolution of all signs and symptoms and improvement or lack of progression of all abnormalities eg on chest radiograph

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Why do we need non-inferiority studies?

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Why do we need non-inferiority studies? Could we run trials versus Placebo?

- Placebo trials are considered unethical for more serious infections with significant morbidity and mortality without treatment
  - Eg, Community Acquired Pneumonia (CAP)
  - Active therapy is effective and would be expected by ethics committees and patients
  - Recent meeting for Anti-infective Drugs Advisory Committee and FDA: Committee voted 13 No 0 Yes to the question: Can placebo-controlled trials be carried out in CAP?

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Why do we need non-inferiority studies? Could we run trials versus Placebo?

- Alternative designs have been suggested
  - Delaying therapy and demonstrating superiority at an early timepoint
  - Including a lower dose of experimental drug which is predicted to be weakly active and demonstrating superiority of higher dose to this
- But these run into ethical issues as well
  - Disease can progress rapidly for some infections
  - Belief that it is important to treat early with an appropriate treatment
  - Justifying a low dose on the basis it is expected to be worse than the higher dose very difficult to do in reality

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Why do we need non-inferiority studies? Could we run trials versus Placebo?

- Placebo trials may be acceptable where spontaneous cure rate is high and outcome is generally positive
  - Acute Bacterial Sinusitis (ABS)
  - Acute Bacterial Exacerbations of Chronic Bronchitis (ABECB)
  - Acute Bacterial Otitis media (ABOM)
- But ethics committees, investigators and patients would need to buy into this
  - Attempts to gain IRB approval for placebo in milder diseases (e.g., sinusitis) have failed

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Why do we need non-inferiority studies? Could we show superiority over current gold standard?

- Current treatments are highly effective
  - For example in CAP (mild-moderate) clinical cure rates are > 90% for Per-Protocol population and >80% for ITT
  - Failures are to some part probably due to them not having a bacterial infection rather than failure of the compound itself
- Not expected to be able to demonstrate superiority in this setting
- If this is the case why do we need more drugs then?
  - Choice eg different formulation, different ae profile
  - Need an option to treat the failures
  - Resistance to current drugs may develop so having further options may help
    - Waiting for this to happen before starting development of the compound could lead to large time gaps in effective treatments

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Controversies of using non-inferiority studies

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Controversies of using non-inferiority studies

- FDA have rejected applications for ABS and AECB because non-inferiority trials were used to demonstrate efficacy
  - For these indications antibiotic treatment has not consistently been superior to placebo in prior trials.
  - Thus non-inferiority to “active comparator” does not demonstrate superiority to placebo
- FDA were challenged by congress to justify why NI trials have been allowed & why NI margins were reasonable

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Controversies: Background

- Antibacterial drugs were discovered a long time ago (Penicillin 1940's)
- These drugs were widely used in clinical practice before robust clinical designs were routinely used
- Data relates to a different era

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The need to bridge to the Past

- Due to issues discussed, all recent studies have been based on non-inferiority trials
  - Prior to 2006 margin based on clinical judgment
- M1 assumption for non-inferiority: active control is more effective than placebo by some known difference (M1)
- This enables us to define a clinically acceptable non-inferiority margin (M2) such that M2 <=M1
- Uncertainty in defining an appropriate margin in infection due to lack of or no information on M1

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The need to bridge to the Past

- Lack of modern data has led to investigation of old data
  - Mary Singer (Division of Antimicrobial Products CDER) has undertaken a thorough review of the data for CAP
  - Considered observation studies 1940's-1960's and controlled trials (not randomised/blinded) 1920's-1960's
  - Data available showed clear benefit of antibiotics but exact quantification difficult

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Limitations of using the old data

- Patient populations are different eg co-morbities
- The disease and/or organisms are different
  - Previously hospitalised patients with pneumococcal pneumonia
  - Now mostly outpatients with a range of organisms
- Endpoints are different
  - Historical data considered mortality
  - Current trials consider cure rates as mortality rates are generally low
- Designs are not robust
- Treatments used in controlled studies no longer used

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Limitations of using the old data

- This leaves us with several issues
- How to map our current studies to these
  - Can we extrapolate this data to other settings?
- Or in fact do we have to match the old populations / endpoints
  - eg severe CAP looking at mortality
  - This could mean no new treatments for other indications (eg where mortality is low)

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Anti-infective Drugs Advisory Committee

- Joint FDA/Infectious Disease Society of America
- Panel of 13 experts
- 2 statisticians:
  - Tom Fleming (based at Washington)
  - Dean Follmann (National Institute of Allergy and Infectious diseases)
- Remit to address the lack of new antibiotics in Community Acquired Pneumonia (CAP)

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Anti-infective Drugs Advisory Committee

- Can historical data be used to set a non-inferiority margin in CAP for IV drugs in hospitalised patients?
  - 13 Yes 0 No
- Can treatment effect be quantified for an NI study of outpatient CAP?
  - 10 Yes 3 (including 2 statisticians) No
- Do you believe the finding of efficacy in more severe CAP supports the drug's effect in less severe CAP?
  - 13 Yes 0 No
  - Implications?
- If NI margin is set for CAP with S Pneumoniae data, can future NI studies include other etiologies?
  - 12 Yes 0 No 1 abstain

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Methodological Controversies

- If we accept that we can conclude that active control is more effective than placebo by some known difference (M1) then the usual controversies remain:-
- Preservation of effect
  - Demonstrating (indirectly) that new treatment is better than placebo is not sufficient
  - Additional requirement of needing to retain a certain amount of the other treatment efficacy (eg 50%)
    - Motivated by concerns re the untestable assumptions of constancy and assay sensitivity or an additional requirement in its own right?
    - Former could imply preservation of effect is additional reassurance so assessing the likelihood of this would be possible
    - Latter suggests it must hold
  - Snappin, SIM 2008 gives a good description of the issues as well as proposing a weighting system directly accounting for departures in these assumptions

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Recent example of setting the margin

Doripenem in Hospital Acquired Pneumonia

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A recent example: Doripenem in HAP

- 2 pivotal P3 trials with primary endpoint of cure rate
  - Trial 1 versus piperacillin/tazobactam;
    - Result: D –Comp 1.5% (-9.1%,12.1%)
  - Trial 2 versus imipenem
    - Result: D –Comp 3.5% (-9.1%,16.1%)
  - Non-inferiority margin of 20% pre-specified
  - During the studies, FDA asked for re-evaluation of the margin
- Multi-step Process
  - Determine treatment effect of the active comparator over placebo (M1)
    a) Estimate rate for placebo
    b) Estimate rate for active comparator
  - Determine NI margin based on a–b
- Company and FDA took a different approach

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Doripenem in HAP: FDA Approach

- No placebo data for clinical response so FDA considered margin based on mortality
- Estimate mortality rate for placebo
  - Observational studies used
  - Inappropriate treatment selected
  - Random effects meta analysis of 4 studies gave rate
    - 59% (40%, 76%)
- Estimate mortality rate for active comparator
  - 4 controlled studies used
  - Random effects meta analysis gave mortality rates
    - piperacillin 18% (11%, 28%)
    - imipenem 17% (13%, 22%)
  - Estimated treatment effect: 40% - 28% =12%
    - CF 41% for difference between estimates
  - => 6% margin for 50% preservation for mortality

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Doripenem in HAP: FDA Approach

- Assumed that treatment effect based on mortality is similar to the treatment effect for clinical response
- Larger NI margin postulated due to endpoint
  - 10% margin

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Doripenem in HAP: Company Approach

- Considered Cure Rates
- Estimate mortality rate for active comparator
  - Meta analysis of 4 controlled studies gave cure rates
    - piperacillin 60.8% (51.6%, 69.9%)
    - imipenem 63% (57.0%, 69.0%)
- Estimate cure rate for placebo
  - Cure rates from observational studies used (as for FDA)
  - Ratio of death rates (inadequate: adequate) calculated as 2.2 and applied to cure rates
    - Piperacillin: 39.2% failure rate so 86.2% placebo failure rate => 13.8% cure rate for placebo
    - Imipenem: 18.6% cure rate for placebo
  - Taking lower limits of active comparator rates 51.6% and 57.0% and placebo cure rate of 20%
    - 50% Preservation of benefit 15.8% and 18.5%

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Alternative Endpoints

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Alternative Endpoints

- Time to response endpoints and PROs have been suggested as way to avoid Non Inferiority
  - By showing new active treatment is superior to standard
- But you would still need to show Non Inferiority for cure rates/mortality
- Endpoint may be possible to use for less severe infections but issues
  - around defining a clinically relevant meaningful difference for the PRO exist
  - no guarantees of showing superiority leaving Non-inferiority issues here as well

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Conclusions

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Conclusions (1)

- Antibacterial drugs were discovered a long time ago and were widely used in clinical practice before robust clinical designs were routinely used
- The potential for resistance to develop to our existing medications as well as giving more choice is the rationale for why more antibiotics are needed
- Non-Inferiority studies are likely to be main approach for serious infections

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Conclusions (2)

- Aim from everyone concerned is to be able to assess drugs using a robust scientific approach so we can approve drugs with a positive benefit risk profile
- Difficulties in this area around defining M1 do make this aim challenging
  - Synthesis of historical data is needed
  - Extrapolation to different endpoints/populations
- Understandably, methods employed by the regulatory authorities for this calculation are likely to be conservative
- The question is whether we can find a way forward in this disease area to balance the requirements above against the need for new antibiotics

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Thank you!

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