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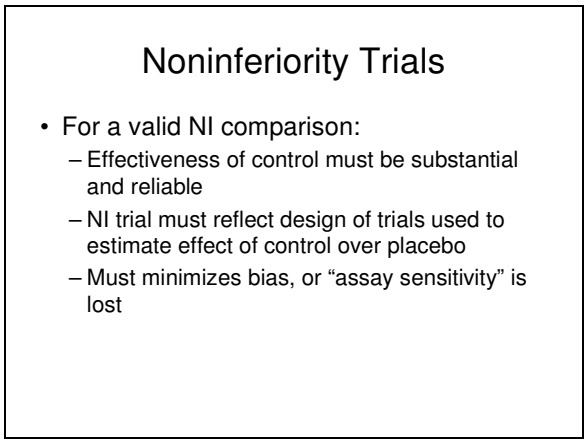
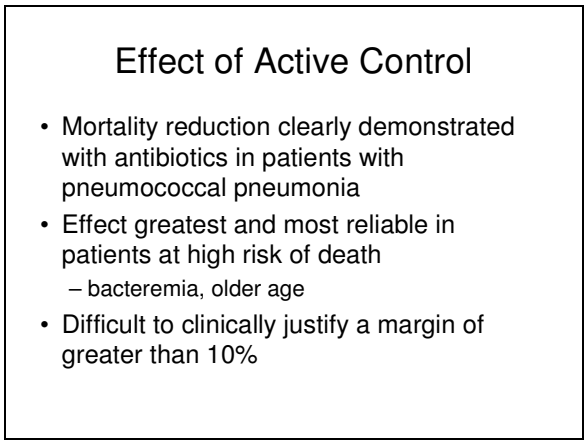
June 2, 2009 Meeting of Anti-Infective Drugs Advisory Committee
Cethromycin for the Treatment of Community-Acquired Bacterial Pneumonia

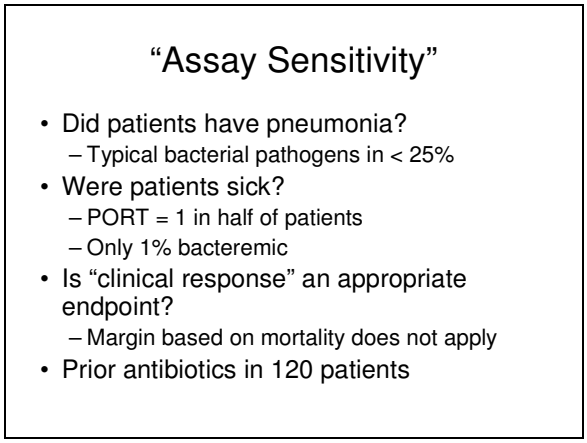
Today, the Anti-Infective Dugs Advisory Committee will consider new drug application 22-398, cethromycin oral tablets for the proposed indication of outpatient treatment of adults with mild to moderate community-acquired pneumonia. Community acquired bacterial pneumonia (CABP) can be a serious disease, and antibiotics have a dramatic treatment effect in patients at high risk for death. Two Phase 3 clinical trials (CL05 and CL06) compared seven-day oral regimens of cethromycin and clarithromycin in patients with CABP. These trials were flawed in ways that make a noninferiority (NI) comparison highly problematic, and preclude any claim of efficacy for cethromycin.



NI trials do not show that two treatments are "equivalent" to each other. Rather, they exclude that one treatment is worse than another by a predefined margin. For the comparison to be valid, a few general criteria need to be met. First, the estimate of the effect of an active control over placebo must be both substantial and reliable. Second, the design of the NI trial must reflect the design of the trials used to compare the active control with placebo. Third, the NI trial must be conducted in a way that minimizes bias, or it loses the ability to detect a difference between the two treatments, also called "assay sensitivity."



A substantial mortality benefit from antibiotics in the treatment of pneumococcal pneumonia is clear from early trials and historical data. This effect is most pronounced in patients at highest risk of death – bacteremic patients over the age of 50.[1] Although different effect sizes have been estimated, it is difficult to clinically justify tolerating more than a 10% increase in mortality with an experimental treatment over an effective control, even if the experimental treatment is safer or more convenient to administer, neither of which are the case for cethromycin.



A number of serious flaws reduce the assay sensitivity of the two trials comparing cethromycin with clarithromycin. Bacterial pathogens were recovered in only one-third of patients, and less than a quarter had "typical" pathogens, raising the possibility that many patients included in the trials did not have pneumonia.[2] Most patients were only mildly ill, reflected by low PORT scores, and only ten (1%) were bacteremic. The primary endpoint in these trials was "clinical cure," as judged subjectively by site investigators. Thus, the population and endpoints in CL05 and CL06 differ substantially from those in the studies used to estimate the effect size of antibiotics in CABP, making a NI comparison difficult, if not impossible.

Another important issue was the prior administration of antibiotics active against *S. pneumonia* in 120 patients, or over 10% of the study population. The allowance of concomitant active therapy along with the inclusion of patients without CABP or who were only mildly ill biases both groups towards similarly high "clinical cure" rates. This reduces or perhaps even eliminates the ability of these trials to distinguish a difference between the two therapies.

1 Fleming TR, Powers JH. Issues in noninferiority trials: the evidence in community-acquired pneumonia. Clin Infect Dis. 2008;47(Suppl 3):S108-20.

[2] "Typical" bacterial pathogens defined as *S. pneumoniae, H. influenzae, and M. catarrhalis*

"Clinically Evaluable"

- Exclusions based on post-randomization events

Subject Disposition	Study CL05-001		Study CL06-001		Studies CL05-001 and CL06-001 Combined	
	Cethromycin 300 mg QD	Clarithromycin 250 mg BID	Cethromycin 300 mg QD	Clarithromycin 250 mg BID	Cethromycin 300 mg QD	Clarithromycin 250 mg BID
Randomized Subjects	292	292	261	261	553	553
Randomized and Dosed	291 (99.7%)	291 (99.7%)	261 (100%)	260 (99.6%)	552 (99.8%)	551 (99.6%)
Completed Study	254 (87.0%)	264 (90.4%)	242 (92.7%)	238 (91.2%)	496 (89.7%)	502 (90.8%)
Discontinued	38 (13.0%)	28 (9.6%)	19 (7.3%)	23 (8.8%)	57 (10.3%)	51 (9.2%)
Primary Reason for Discontinuation						
Adverse Event	10 (3.4%)	10 (3.4%)	4 (1.5%)	9 (3.4%)	14 (2.5%)	19 (3.4%)
Clinical Failure	8 (2.7%)	4 (1.4%)	8 (3.1%)	5 (1.9%)	16 (2.9%)	9 (1.6%)
Lost to Follow-up	7 (2.4%)	4 (1.4%)	0	0	7 (1.3%)	4 (0.7%)
Withdrew Consent	6 (2.1%)	3 (1.0%)	4 (1.5%)	4 (1.5%)	10 (1.8%)	7 (1.3%)
Other	7 (2.4%)	7 (2.4%)	3 (1.1%)	5 (1.9%)	10 (1.8%)	12 (2.2%)

Also, nearly 15% of patients were excluded from the per protocol analysis, also called the "clinically evaluable" population, because of loss to follow-up, premature discontinuation of therapy, use of non-study antibiotics, intercurrent illness, or other protocol violations. The exclusion of such a large number of patients due to post-randomization events results in an effective loss of randomization, turning these trials into mere observational studies. Importantly, the rate of these exclusions was higher in the cethromycin group than in the clarithromycin group, raising the possibility of a systematic bias.

Table 6.3: Primary Outcome Analyses

Analysis Population	Cethromycin cure/N (%)	Clarithromycin cure/N (%)	Treatment Difference, (95% CI) [a]
Study CL05			
ITT (n=515)	217/261 (83.1)	206/254 (81.1)	2.0 (-5.0, 9.0)
CE (n=426)	205/218 (94.0)	195/208 (93.8)	0.3 (-4.7, 5.3)
Study CL06			
ITT (n=510)	213/257 (82.9)	224/253 (88.5)	-5.7 (-12.1, 0.8)
CE (n=445)	205/224 (91.5)	212/221 (95.9)	-4.4 (-9.3, 0.5)

Despite these flaws, what does the analysis reveal? In one of the two trials, CL06, the treatment difference between cethromycin and clarithromycin did not exclude a margin of 10%. In other words, this trial did not demonstrate NI. The discrepant findings in the two identically-designed trials likely reflects the unreliability of the outcome measure used and poor study design.

Table 6.5: FDA Sensitivity Analysis – Primary Endpoint

Analysis Population	Cethromycin cure/N (%)	Clarithromycin cure/N (%)	Treatment Difference, (95% CI) [a]
Study CL05			
ITT (n=515)	89/110 (80.9)	95/121 (78.5)	2.4 (-8.8, 13.6)
CE (n=426)	84/89 (94.4)	89/93 (95.7)	-1.3 (-8.7, 6.1)
Study CL06			
ITT (n=510)	86/113 (76.1)	90/105 (85.7)	-9.6 (-20.9, 1.6)
CE (n=445)	85/98 (86.7)	86/92 (93.5)	-6.7 (-16.2, 2.7)

What happens if you exclude patients with a PORT score of 1, those with atypical pathogens, and those who received prior antibiotic therapy? You exclude over half the patients and arrive at what should have been the study population in the first place. In CL06, the point estimates for clinical cure appear to be even worse than before, and even a 20% increase in the clinical failure rate with cethromycin is not excluded in the ITT population.

Safety and Convenience

- Hepatotoxicity?
  - Telithromycin (KETEK)
    - Another ketolide antibiotic, very hepatotoxic
  - LFT signal
- Increased rate of dysgeusia (9% vs 4%)

Putting aside efficacy for a moment, I am concerned with the real possibility that cethromycin may be hepatotoxic. The ketolide antibiotic telithromycin (KETEK) has been associated with an alarmingly high rate of acute liver failure, prompting concerns with cethromycin, another drug in the same class.[3] Although not associated with any cases of hepatotoxicity fulfilling Hy's law, cethromycin was associated with a higher rate of transaminase elevations > 3x the upper limit of normal.[4] Given the rarity of drug-induced liver injury, the absence of any cases of liver failure in a small safety population does not reassuringly exclude the possibility of hepatotoxicity. With regard to side effects, cethromycin was associated with more dysgeusia than clarithromycin (9% vs 4%) in the two Phase 3 trials. For a drug that may potentially be hepatotoxic and offers no convenience advantage, it becomes difficult to justify tolerating anything less than superiority over another effective antibiotic, let alone questionable NI findings.

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3 Graham DJ. Telithromycin and acute liver failure. N Engl J Med. 2006 Nov 23;355:2260-1.

[4] Cethromycin: ALT > 3x ULN 0.9%, AST > 3x ULN 1.1%. Clarithromycin: ALT > 3x ULN 0.2%, AST> 3x ULN 0.2%.

Macrolide-Resistant Pathogens

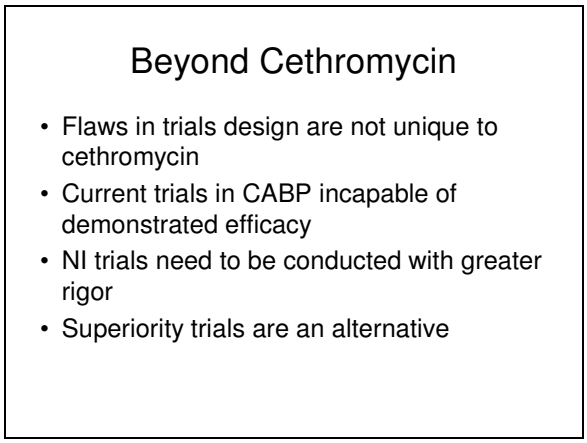
- Sponsor argues for a role in the treatment of resistant pathogens
  - Where are the clinical data?

The sponsor has argued that cethromycin is needed to combat macrolide- and other drug-resistant pathogens. However, no clinical data for efficacy in patients with these resistant pathogens has been presented.

Summary

- Efficacy findings questionable
  - No "assay sensitivity," wrong endpoint
- What are the benefits?
  - No evidence for efficacy in drug-resistant cases
  - Possible hepatotoxicity signal
- Little basis for a noninferiority comparison
- One was done and margin was not met

To summarize, the clinical trials presented today were seriously flawed, making it difficult to determine any differential treatment effect in the mildly ill patients studied. Indeed, despite the lack of a basis for a NI comparison, cethromycin was found to be *nearly worse than* clarithromycin in one trial. Certainly, when the analysis is restricted to patients at higher risk of treatment failure and death, neither trial established the NI of cethromycin by any reasonable margin. Given the possibility of a signal for hepatotoxicity and the lack of any clinical data demonstrating efficacy in patients with resistant pathogens, there is no rationale for approving this drug on the basis of noninferiority.



Unfortunately, the flaws in study design discussed today are not unique to cethromycin, but plague nearly all recent clinical trials of new antibiotics for the treatment of CABP. Enrolling patients without the disease in question or who are not ill, allowing concomitant active therapy, excluding large numbers of patients from analysis, and evaluating the wrong outcomes bias these trials towards a finding of NI, but prevent any determination of a differential treatment effect. Conducting poorly designed trials in this manner does not serve patients well, and presents the likely scenario that an ineffective antibiotic will be declared effective and enter clinical use. It does not serve sponsors well either, as money and time are wasted on trials that are incapable of establishing efficacy.

What is the next step for cethromycin? If additional noninferiority trials are conducted, they must be designed far more rigorously and evaluate mortality in an appropriate high-risk population. Alternatively, measuring a validated and clinically relevant outcome other than mortality in a superiority trial could avoid many of the pitfalls of NI trials, while providing the substantial evidence for efficacy necessary to meet regulatory and scientific standards.