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Short Communication

Macrolide therapy for community-acquired pneumonia due to atypical pathogens: outcome assessment at an early time point

Thomas M. File Jr [a,b,*], Paul B. Eckburg [c], George H. Talbot [d], Lily Llorens [e], H. David Friedland [e]

[a] Summa Health System, Akron, OH, USA
[b] Northeast Ohio Medical University, Rootstown, OH, USA
[c] Division of Infectious Diseases, Stanford University School of Medicine, Stanford, CA, USA
[d] Talbot Advisors, Anna Maria, FL, USA
[e] Cerexa, Inc., Oakland, CA, USA

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ABSTRACT

Background: Therapy directed against atypical pathogens in patients with community-acquired pneumonia (CAP) is often recommended. This post-hoc analysis evaluated the effect of addition of a macrolide to ceftaroline fosamil or ceftriaxone treatment in atypical CAP.

Methods: Two phase 3, double-blind, comparative safety and efficacy studies of ceftaroline fosamil vs. ceftriaxone, FOCUS 1 and FOCUS 2, enrolled adults with CAP. Only FOCUS 1 included 24-h adjunctive clarithromycin therapy for all patients on day 1. Day 4 and test-of-cure (TOC) outcomes were compared for adjunctive vs. no adjunctive therapy.

Results: Of 1240 enrolled patients, 130 patients with CAP due to atypical pathogens alone were included (FOCUS 1, $n = 64$; FOCUS 2, $n = 66$). Among patients infected with *Mycoplasma pneumoniae* and/or *Chlamydophila pneumoniae* alone, a higher clinical response rate was observed with clarithromycin plus ceftaroline fosamil or ceftriaxone compared with treatment without additional clarithromycin at day 4 [38/49 (77.6%; FOCUS 1) vs. 24/43 (55.8%; FOCUS 2)], but not at the TOC assessment [42/49 (85.7%; FOCUS 1) vs. 41/43 (95.3%; FOCUS 2)]. In patients infected with *Legionella pneumophila* alone, a higher clinical response rate with adjunctive clarithromycin therapy was observed at the TOC assessment alone [12/12 (100%; FOCUS 1) vs. 14/19 (73.7%; FOCUS 2)]. The unadjusted odds ratio of a favourable clinical response at day 4 with adjunctive clarithromycin vs. no adjunctive clarithromycin was 2.4 (95% confidence interval 1.1–5.1; $P = 0.0299$) for all pathogens combined.

Conclusions: These results suggest that empirical antibiotic therapy against atypical pathogens may improve early clinical response rate. This hypothesis is best evaluated in a prospective trial.

1. Introduction

Community-acquired pneumonia (CAP) treatment guidelines from the Infectious Diseases Society of America (IDSA)/American Thoracic Society (ATS) recommend treatment for atypical pathogens (*Mycoplasma pneumoniae*, *Chlamydophila pneumoniae* and *Legionella pneumophila*) with a macrolide (azithromycin, clarithromycin or erythromycin), doxycycline or a fluoroquinolone [1]. Variable reduction in mortality has been shown using empirical therapy for CAP with the addition of atypical pathogen coverage in randomized controlled trials [2–4] and observational studies [5]. A recent trial demonstrated that patients with atypical CAP were less likely to reach clinical stability at day 7 with β-lactam monotherapy compared with β-lactam and macrolide combination therapy [hazard ratio 0.33; 95% confidence interval (CI) 0.13–0.85; $P = 0.02$] [6]. Based largely on typical community-acquired bacterial pneumonia (CABP) responses and in agreement with historical and contemporary data [7,8], 2014 US Food and Drug Administration (FDA) guidance for CABP recommends efficacy assessment at 3–5 d after treatment initiation, earlier than recommended previously [9].

Ceftaroline fosamil is indicated for the treatment of CABP caused by selected typical pathogens based on results from two pivotal phase 3 studies—FOCUS 1 (NCT00621504) and FOCUS 2 (NCT00509106)—which had identical designs with the exception of a 24-h course of adjunctive clarithromycin on day 1 of treatment in FOCUS 1 [10,11]. FOCUS 2 was conducted in study centres in Asia, Europe and South America, where treatment guidelines do not always recommend the addition of a macrolide to β-lactam therapy for the treatment of CABP [12,13]. The objective of this post-hoc

* Corresponding author. Summa Health System, 75 Arch St, Suite 506, Akron, OH 44304, USA.
E-mail address: filet@summahealth.org (T.M. File Jr).

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subset analysis was to evaluate any potential effect of adjunctive clarithromycin therapy on early (day 4) clinical stability and symptom response, and compare that with the investigator-determined clinical response at test-of-cure (TOC) assessment in patients with CAP infected with atypical pathogens alone, specifically by comparing results from FOCUS 1 (which included initial adjunctive macrolide therapy) with those from FOCUS 2 (no adjunctive atypical therapy).

2. Materials and methods

2.1. Study design

FOCUS 1 and 2 were phase 3, global, multicentre, randomized, double-blind, comparative safety and efficacy studies of intravenous ceftaroline fosamil vs. intravenous ceftriaxone; both studies have been described previously [11,14]. FOCUS 1 included 24-h adjunctive clarithromycin on day 1; FOCUS 2 did not include adjunctive clarithromycin therapy. Patients were assigned at random on a 1:1 basis to the ceftaroline fosamil or ceftriaxone group, and cephalosporin treatment was administered for 5–7 d. For both studies, each patient or their legally authorized representative was required to provide written informed consent, including willingness and ability to comply with all study procedures. Before study initiation, all sites received approval for study conduct from their independent ethics committee or institutional review board.

2.2. Patient and disease characteristics

Eligibility criteria for both studies (summarized in Appendix A of the Supplementary material) have been described previously [10,11]. Briefly, adult patients with CAP that was severe enough to require hospitalization and intravenous therapy with a Pneumonia Patient Outcomes Research Team (PORT) risk class of III or IV were eligible for inclusion. Criteria used in the diagnosis of atypical pathogens are summarized in Table A of the Supplementary material. A positive urinary antigen test for *L. pneumophila* serotype 1 at baseline resulted in exclusion from both trials; however, Legionella infection could be diagnosed subsequently in the enrolled population using acute and convalescent serology criteria (Table A of the Supplementary material).

2.3. Post-hoc analysis

This post-hoc analysis assessed outcomes for all patients presenting with atypical pathogens alone (single or mixed), specifically *M. pneumoniae*, *C. pneumoniae* and *L. pneumophila*. A potential clinical effect of administering 24-h adjunctive clarithromycin therapy was assessed by comparing grouped results of FOCUS 1 with FOCUS 2. We analysed the two population groups for clinical stability and pneumonia-specific symptom improvement (S&S) response at day 4 and investigator-determined response at the TOC time point (clinical response at TOC).

The FDA criteria for favourable S&S response at day 4 were assessed using clinical stability determined by temperature ≤37.8 °C, heart rate ≤100 bpm, respiratory rate ≤24 breaths/min, systolic blood pressure ≥90 mmHg, oxygen saturation ≥90%, normal mental status and symptom improvement, defined as improvement from baseline in at least one symptom (cough, dyspnoea, pleuritic chest pain, sputum production) and no worsening of any other components. Clinical cure was defined as total resolution of all signs and symptoms of pneumonia, or sign and symptom improvement to an extent that no further antimicrobial therapy was necessary.

2.4. Multivariate analysis

To further investigate the differential favourable S&S response rate observed at day 4 in patients with atypical CAP who received 24 h of clarithromycin, a three-stage exploratory multivariate logistic regression was performed to account for baseline characteristics in the two studies that could be predictive of or influence response (summarized in Appendix B of the Supplementary material).

3. Results

3.1. Study patients

In total, 613 patients were enrolled in FOCUS 1 at 114 study centres in 21 countries, and 627 patients were enrolled in FOCUS 2 at 84 centres in 14 countries. Of these, 64 patients from FOCUS 1 and 66 patients from FOCUS 2 presented with atypical pathogens alone. Patient demographics and baseline characteristics for this subset of the overall study population are provided in Table 1.

Table 1
Demographics and baseline characteristics in patients with atypical pathogens alone in the FOCUS studies (modified intent-to-treat efficacy population).

Characteristic, *n* (%)	FOCUS 1 (*n* = 64)[a]	FOCUS 2 (*n* = 66)[a]
Mean age (years)		
<65	44 (68.8)	47 (71.2)
≥65	20 (31.3)	19 (28.8)
Male	45 (70.3)	37 (56.1)
PORT risk class		
III	46 (71.9)	50 (75.8)
IV	18 (28.1)	16 (24.2)
Smoking history	32 (50.0)	29 (43.9)
Fever (>38 °C orally or >38.5 °C rectally or tympanically)	50 (78.1)	42 (63.6)
Hypoxaemia (PaO_2 <60 mmHg or O_2 saturation <90%)	24 (37.5)	31 (47.0)
Pleural effusion[b]	12 (18.8)	3 (4.5)
Pulmonary infiltrate status		
Unilobar	45 (70.3)	53 (80.3)
Multilobar	19 (29.7)	13 (19.7)
Region of enrolment		
Eastern Europe	29 (45.3)	36 (54.5)
Western Europe	21 (32.8)	17 (25.8)
Africa	6 (9.4)	0
Asia	3 (4.7)	4 (6.1)
USA	3 (4.7)	0
Latin America	2 (3.1)	9 (13.6)
Met modified IDSA/ATS criteria for severe CABP[c]	18 (28.1)	19 (28.8)
Met SIRS criteria[d]	56 (87.5)	46 (69.7)
Prior single dose of ciprofloxacin[e]	7 (10.9)	1 (1.5)
Prior single dose of clarithromycin[e]	1 (1.6)	1 (1.5)

ATS, American Thoracic Society; CABP, community-acquired bacterial pneumonia; FOCUS, ceFtarOline Community-acquired pneUmonia trial versuS ceftriaxone in hospitalized patients; IDSA, Infectious Diseases Society of America; PaO_2/FiO_2 ratio, ratio of arterial oxygen partial pressure to fractional inspired oxygen; PORT, Pneumonia Patient Outcomes Research Team; SIRS, systemic inflammatory response syndrome; WBC, white blood cell.

[a] Includes the combined group of patients treated with ceftaroline fosamil or ceftriaxone; in FOCUS 1, patients also received clarithromycin therapy on day 1 of the study.

[b] Pleural effusion includes patients with pleural effusion of any size on the right or left side.

[c] Defined as presence of at least three of the following: respiratory rate >30 breaths/min; WBC count <4000 cells/mm^3; PaO_2/FiO_2 ratio ≤250; multilobar infiltrates; confusion/disorientation; blood urea nitrogen level ≥20 mg/dL; platelet count <100,000 cells/mm^3; temperature <36 °C; or hypotension requiring aggressive fluid resuscitation.

[d] Defined as presence of at least two of the following: temperature <36 °C or >38 °C; heart rate >90 bpm; respiratory rate >20 breaths/min; WBC count <4000 or >12,000 cells/mm^3; or immature neutrophils >10%.

[e] Patients were permitted to receive a single dose of a single short-acting antibiotic according to the investigator's clinical judgement within 96 h of receiving the first dose of study drug. The only administered prior short-acting antibacterial agents with atypical CAP activity in either study were ciprofloxacin (fluoroquinolone) and clarithromycin (macrolide). No other antibiotics with atypical activity were administered as prior antibiotics (e.g. oxazolidinones, tetracyclines, long-acting fluoroquinolones, long-acting macrolides).