Clinical applications of azithromycin microspheres in respiratory tract infections

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Abstract: Few adequately designed clinical trials have addressed optimal treatment duration in lower respiratory tract infections. Drugs possessing favourable pharmacokinetic and pharmacodynamic profiles may obtain early bacterial eradication allowing shorter treatment duration. This may be associated with a number of advantages including reduced resistance induction, increased compliance, lesser adverse events, and cost containment. Recently, a novel 2.0 g single dose of azithromycin microspheres has been compared with 7-day levofloxacin 500 mg or extended release clarithromycin in over 400 patients with community-acquired pneumonia. Clinical cure and bacteriological eradication rates, hospitalizations, and deaths were similar between azithromycin and comparators. Azithromycin 2.0 g microspheres proved as effective as 7 days of levofloxacin 500 mg in acute exacerbation of chronic bronchitis patients across all degrees of obstruction severity. In both settings Azithromycin microspheres obtained clinical cure in most patients harbouring macrolide-resistant *Streptococcus pneumoniae* strains. The drug was well tolerated in clinical studies and in healthy volunteers with modest and transitory adverse events. An undoubted advantage of single-dose azithromycin administration is the facility in ensuring that patients complete their prescribed course of therapy. A further advantage of single-dose therapy is the potential for use as directly-observed therapy, which may be useful in specific clinical conditions.

Keywords: azithromycin microspheres, pneumonia, COPD exacerbations

Introduction

The last 50 years have witnessed an impressive evolution in the antibiotic armamentarium at the clinician's disposal. The availability of effective antibiotic treatment has substantially impacted on overall mortality of patients with lower respiratory tract infections (LRTIs). International guideline drafting and implementation have been important in highlighting key factors in improving care in community-acquired pneumonia (CAP) and acute exacerbation of chronic bronchitis (AECB) (Woodhead et al 2005; Mandell et al 2007). Remarkably, guidelines contain few indications regarding the appropriate duration of antibiotic therapy. This reflects the paucity of appropriately designed large scale clinical trials addressing such an important treatment issue. Conventionally, antibiotics are continued until clinical and laboratory indices of infection are normal in patients with LRTIs. It is recognized that patients tend to interupt treatment once they feel better, decreasing compliance to treatment after that time point.

Antibiotic exposure is unavoidably associated with the phenomenon of antibiotic resistance due to a selection pressure on bacterial strains with natural or acquired resistance. Ideally, antibiotics should be maintained only up until bacteria are effectively cleared as further protraction of therapy increases unnecessary bacterial exposure to drugs. Currently, antimicrobial resistance is a global problem resulting in high hospitalization rates, mortality and costs in LRTIs (Sahm 2003). It has been suggested that shortening antimicrobial treatment duration may benefit resistance patterns.

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For example, low dose and prolonged duration of β-lactam antibiotic treatment may contribute to promoting pharyngeal carriage of drug-resistant *Streptococcus pneumoniae* (Guillemot et al 1998), whereas high-dose short course amoxicillin may be associated with significantly lower penicillin-resistant *S. pneumoniae* carriage (Schrag et al 2001).

Patient adherence to prescribed antibiotic regimens is affected by variables including dosing interval, treatment duration, adverse effects, and palatability in pediatric patients. Adherence to once-daily regimens has been shown to be far superior to that of twice- (Kardas 2007) or thrice-daily dosing schemes (Claxton et al 2001). It is fairly well established that patient compliance with antibiotic therapy begins to drop after 3–7 days of treatment (Kardas 2002). Additional potential benefits of short course antibiotic therapy in LRTIs patients include diminished impact on human endogenous flora, decreased total drug exposure with reduced side effects, reduced health care worker time expenditure, and reduced costs.

In order to avoid falling short of effectively controlling infection, short-course antibiotic therapy should be based on robust pharmacokinetic and pharmacodynamic considerations. Candidate drugs for short-course regimens should be able to achieve adequate tissue penetrations and concentrations at the site of infection for a sufficiently long length of time to ensure bacterial eradication (Nicolau 2001). The development of an effective short course regimen requires a concentration-dependent antimicrobial effect. The rate and extent of bacterial killing increase with increasing drug concentrations. For such agents the pharmacodynamic/pharmacokinetic predictors of efficacy are the area under the concentration-time curve/MIC ratio (AUC/MIC) and the maximal serum drug concentration/MIC ratio (C_{max}/MIC) (Nicolau 2001).

Short-course azithromycin treatment in lower respiratory tract infections

Azithromycin is an azalide antibiotic exerting activity against most pathogens commonly involved in LRTIs. It acts by interfering with bacterial protein synthesis through binding of the 50S ribosomal subunit of susceptible microorganisms. Azithromycin is an ideal candidate for short-course antibiotic regimens for a number of reasons. Compared with earlier macrolides, azithromycin shows improved pharmacokinetic/dynamic properties that determine a prolonged half-life and excellent tissue penetration. The drug rapidly moves from the bloodstream into the interstitial compartment resulting in low serum concentrations but high and persistent tissue concentrations (Amsden et al 1997). Characteristically, azithromycin concentration in lung tissue may be over a 100-fold greater than in the circulation. High tissue concentrations are maintained for extended periods of time due to slow release. Considering that respiratory tract infections reside in the interstitial space, tissue accumulation of azithromycin may guarantee high drug concentrations in the active site of infection. A further interesting characteristic is the ability of azithromycin to concentrate within inflammatory cells, particularly neutrophils and monocytes within the bloodstream, and tissue macrophages (Mandell et al 2001). The ongoing inflammatory process in the lung recalls azithromycin-laden neutrophils from the circulation which then unload the drug in the presence of bacteria within inflammation sites (Hand et al 2001). Inflammatory cells therefore act as a "Trojan horse" delivering local concentrations of azithromycin that are several orders of magnitude greater than that in plasma. Neutrophil unloading and the extended half life of azithromycin (~60 hours) sustain therapeutic drug concentrations at the site of infection for prolonged periods of time (Blumer 2005). Furthermore, inflammatory cell uptake of azithromycin is non-saturable and concentration dependent, suggesting that administration of higher doses of the drug early in the course of the infection may result in even greater drug concentration at the sites of infection.

Short-course treatment of CAP patients with azithromycin has been shown to be effective, with the 3-day (500 mg single daily dose) regimen and the 5-day (500 mg first day, 250 mg following days) regimens obtaining comparable results (Socan 1998). Clinical studies have shown that a 3-day or 5-day treatment with azithromycin is at least as effective as more prolonged regimens of benzylpenicillin or erythromycin (Bohte et al 1995), and clarithromycin (O'Doherty et al 1998). Azithromycin and comparators were similar in terms of clinical, microbiological, and radiological results in outpatient or hospitalized cases of mild-to moderate CAP. Similarly, 3 or 5-day azithromycin regimens were clinically and microbiologically as effective as more prolonged treatment with amoxicillin-clavulanic acid (Hoepelman et al 1997), levofloxacin (Amsden et al 2003), clarithromycin (Bradbury et al 1993) or 5-day courses of moxifloxacin (DeAbate et al 2000) or dirithromycin (Castaldo et al 2003) in patients with AECB. Table 1 shows a summary of clinical data for the quoted studies on azithromycin versus comparators in LRTIs.

Given its prolonged half-life, propensity to accumulate in tissues and inflammatory cells, and post antibiotic effect,

Table 1 Clinical success rates in studies evaluating azithromycin against comparators in the treatment of lower respiratory tract infections

First author, year	Setting	Azithromycin dosing scheme	Comparator/s dosing scheme	No. of treated patients	Clinical success rate
Bohte 1995	CAP	500 mg once daily, 3 days	Benzylpenicillin i.v. Erythromycin	35 azitromycin vs 29 benzylpenicillin 19 azithromycin vs 21 erythromycin	Azithromycin 83% vs Benzylpenicillin 66% Azithromycin 79% vs Erythromycin 76%
O'Doherty 1998	CAP	500 mg once daily, 3 days	Clarithromycin 250 mg twice daily, 10 days	101 azithromycin 102 clarithromycin	Azithromycin 94% Clarithromycin 95%
Bradbury 1993	LRTI	500 mg once daily, 3 days	Clarithromycin 250 mg twice daily, 10 days	252 azithromycin 258 clarithromycin	Azithromycin 94% Clarithromycin 97%
Hoepelman 1997	LRTI	500 mg once daily, 3 days	Amoxi/clav acid 625 mg 3 times daily, 10 days	62 azithromycin 61 amoxi/clav acid	Azithromycin 95% Amoxi/clav 90%
DeAbate 2000	AECB	500 mg day 1, 250 mg days 2–5	Moxifloxacin 400 mg once daily, 5 days	243 azithromycin 221 moxifloxacin	Azithromycin 92% Moxifloxacin 90%
Amsden 2003	AECB	500 mg day 1, 250 mg days 2–5	Levofloxacin 500 mg once daily, 7 days	118 azithromycin 117 levofloxacin	Azithromycin 89% Levofloxacin 92%
Castaldo 2003	AECB	500 mg day 1, 250 mg days 2–5	Dirithromycin 500 mg once daily, 5 days	46 azithromycin 40 dirithromycin	Azithromycin 86.5% Dirithromycin 95.5%

Abbreviations: CAP, community-acquired pneumonia; LRTI, lower respiratory tract infections; AECB, acute exacerbations of chronic bronchitis; Amoxi/clav, amoxicillin/clavulanic acid.

attempts have been made to condense conventional treatment into single large dose schemes of azithromycin (1.5 g in adults, 30 mg/kg in children) for the management of LRTIs. Administration of a single, higher dose of azithromycin has been shown to achieve more rapid bacterial eradication and enhanced survival than the same dose divided over several days in pre-clinical infection models of otitis media, murine pneumonia and septicemia (Girard et al 2005, Babl et al 2002). This suggests that antibiotic "front-loading", attaining higher systemic exposure early in the course of infection (ie, the AUC from time zero to 24 hours [AUC_{0-24}] post dosing), may result in more rapid and efficient bacterial clearance following the single-dose regimen. This may offer benefits in terms of minimizing emergence of resistance.

In an open randomized study, the efficacy and safety of a single 1.5 g oral dose of azithromycin was compared with the standard 3-day regimen in the treatment of 100 patients with community-acquired atypical pneumonia (Schönwald et al 1999). Clinical success was obtained in 97.9% of patients in both groups. Side effects were observed in 2 patients in the single-dose group, and one patient in the 3-day group. Due to the relatively small number of patients studied, the safety evaluation of the single-dose regimen is inconclusive. However, the study does indicate that a single 1.5 g dose of azithromycin may be an alternative to the standard 3-day azithromycin regimen in the treatment of outpatients with atypical pneumonia syndrome. A later study analyzed the serum and white blood cell pharmacokinetic behavior of 1.5 g

single dose azithromycin compared to the same dose over 3 days (Amsden et al 2001). The single drug bolus resulted in significantly higher peak serum concentration compared to the 3-day regimen, although the subjects' overall drug exposure did not differ significantly. At 10 days from the start of therapy both regimens showed intracellular white blood cell concentrations that were above the MIC_{90} values of the vast majority of community-acquired respiratory pathogens.

The highest single oral dose of azithromycin currently approved is an immediate-release 2.0 g sachet formulation of oral powder for suspension in the treatment of chlamydial and gonococcal urethritis and cervicitis (Handsfield et al 1994). The reported 34% incidence of nausea and 14% incidence of diarrhea indicate that this formulation is likely to achieve limited clinical diffusion due to the high level of gastrointestinal intolerance.

Azithromycin microsphere formulation

Recently, microspheres have been developed as a means of effectively delivering antibiotics in periodontal (Paquette 2007) and ocular diseases (Pijls et al 2006), for minimizing toxicity of antimycobacterial treatment (Rastogi et al 2006), and as an aid in *Helicobacter pylori* eradication (Patel et al 2007). A novel azithromycin microsphere formulation (recently approved as Zmax in the USA) has been developed to address the challenge of administering a higher oral dose of the drug as a single dose while maintaining

tolerability. The characteristics of the microspheres, with a mean diameter ranging from approximately 100–300 μm, were selected based on a combination of palatability, release profile, and manufacturability. Azithromycin is released slowly via diffusion through pores formed in-situ in the microspheres. Alkalinizing agents (sodium phosphate tribasic and magnesium hydroxide) were incorporated in the formulation. Following ingestion, the alkaline nature of the microsphere formulation delays initial release of drug in the stomach. Azithromycin is thus released over 2 hours after ingestion in the small intestine. This allows by-passing of the motilin receptors in the upper gastrointestinal tract. Local drug activation of the motilin receptors is thought to mediate much of the macrolide-related gastrointestinal side effects (Takeshita et al 2006). Motilin receptor density is maximal in the antrum and decreases in the aboral direction. All the drug is released prior to the colon, thus ensuring maximal bioavailability (approximately 83%) (Chandra et al 2007). In an open-label, randomized, parallel-group study of 24 healthy adult subjects the pharmacokinetic profiles of azithromycin given as 2.0 g microspheres were characterized in serum and white blood cells and compared with those of a 3-day regimen totaling 1.5 g (Liu et al 2007). Compared with the conventional 3-day 1.5 g azithromycin treatment, the single-dose 2.0 g microsphere formulation obtained a 2-fold higher maximum plasma concentration (C_{max}) and a 3-fold higher 24-hour area under the concentration-time curve ($AUC_{0–24}$) at day 1. The total systemic exposure in serum over 5 days following the start of dosing ($AUC_{0–120}$) was similar for the two regimens. Similarly, in white blood cells, threefold higher drug exposure and maximal concentrations were found at day 1 following single dose administration compared with the 3-day regimen.

In an observer-blind, parallel group, single-dose study, the tolerability profiles of azithromycin 2.0 g microspheres were compared with the immediate-release azithromycin 2.0 g sachet formulation of oral powder for suspension (Chandra et al 2007). This was a complex study that also evaluated pharmacokinetic profiles of the two compounds and the effect of food (high fat meal and a standard meal) and an antiacid on the rate of drug absorption. A total of 377 healthy male and female volunteers were recruited. Compared with the sachet oral powder suspension, the microsphere formulation was associated with a slower absorption rate (57% decrease in mean C_{max} with a 2.5 hour delay in time to reach C_{max}). However, because the AUC values were comparable, overall drug exposure was similar. The incidence of gastrointestinal side effects (abdominal pain, nausea, vomiting, and diarrhea) was significantly lower with azithromycin microspheres compared to the immediate-release formulation. One non-gastrointestinal adverse event common to azithromycin slow-release and immediate release was headache (12% and 6%, respectively). In both groups over 90% of adverse events were mild in intensity and occurred within the first 2 hours after dosing. Both the high fat meal and the standard meal increased the rate of drug absorption (2-fold higher C_{max} values, and 2- to 4-hour shortening of time to maximal concentration) but were associated with an increased incidence of nausea and vomiting. It was assumed that meal-triggered gastric acid secretions led to faster release of azithromycin from the microspheres (Chandra et al 2007). Because of the decreased tolerability of the formulation when taken with food, it was suggested that azithromycin microspheres be taken on an empty stomach. Pharmacokinetic properties of the azithromycin microspheres were not significantly affected by co-administration of an antiacid.

Azithromycin microspheres in community-acquired pneumonia

Two phase III multinational, multicenter, double-blind, double-dummy studies analyzed the efficacy and safety of a new microsphere (MS) formulation of azithromycin, 2.0 g given as a single dose, compared with either the extended-release formulation of clarithromycin) (1 g od for 7 days) (Drehobl et al 2005) or with levofloxacin (500 mg od for 7 days) (D'Ignazio et al 2005) in the treatment of adults with mild-to-moderate CAP.

In the clarithromycin extended-release comparator trial, eligible subjects were required to be 16 years of age or older, with cough productive of sputum and a diagnosis of pneumonia as demonstrated by two or more of the following signs or symptoms: auscultatory findings on pulmonary examination of rales and/or evidence of pulmonary consolidation; dyspnea or tachypnea; body temperature >38 °C (oral); or an elevated total peripheral white blood cell count (>10,000/mm³) or >15% immature neutrophils (bands). In addition, subjects had to have a prospectively calculated Modified Fine Risk score of ~70 (Fine Classes I and II) (Fine et al 1997). A total of 501 subjects were randomized and 499 were treated. Patients were recruited at 58 centers in 7 countries among the US, Canada, Europe, and Asia. In the levofloxacin trial, subjects were aged 18 years or older with a clinical diagnosis of mild-to-moderate CAP with a Fine mortality risk class of I, II, or III (ie, a risk score of ~90). In total, 427 patients were randomized, of whom 423 received study medication. Patients were enrolled at 56 centers in 8 countries among North and South America, Europe, and Asia.

In both studies, clinical assessments were conducted at baseline (Day 1), during treatment (Days 3–5), at the end of treatment (Days 8–11), post treatment at the test of cure (TOC) visit (Days 14–21) and at a long-term follow-up visit (Days 28–35). Clinical efficacy was assessed at the TOC visit. Subjects with a clinical response of cure at the TOC visit were assessed for relapse at the long-term follow-up visit (Days 28–35). Bacteriological response was assessed in those subjects from whom a pathogen was identified at baseline. Table 2 shows the demographics and baseline characteristics of the patients enrolled in the two studies. No differences in terms of either clinical response or bacteriological response were noted between azithromycin microspheres and comparators at the TOC visit (Days 14–21) (Table 3).

In the azithromycin vs clarithromycin study, at the long-term follow-up visit (days 28–35), only 1 subject (0.6%) in the azalide study arm and 5 subjects (2.8%) in the clarithromycin study arm were classified as having relapsed. Clinical cure rates in patients with multilobar pneumonia were only slightly lower than those in patients with single lobe pneumonia (88.5% vs 94.4%). Two azithromycin-treated subjects and one clarithromycin-treated subject were hospitalized for worsening of pneumonia. In this study there were 4 deaths, all of which were in the clarithromycin extended release arm. None of the deaths were attributed to study therapy or progression of CAP. In the study comparing azithromycin microspheres with levofloxacin, 6 subjects (2 azithromycin and 4 levofloxacin) were hospitalized for worsening pneumonia; 2 of the levofloxacin-treated and 1 of the azithromycin-treated subjects ultimately died of causes other than pneumonia.

In the azithromycin vs clarithromycin study a pathogen was identified in 281/499 (56%) of treated patients, with evidence of mixed infection in 16%. An atypical pathogen was identified in 24% of azithromycin-treated subjects. In the azithromycin vs levofloxacin study a pathogenic microrganism was identified in 219/423 (52%) of treated patients, a mixed infection being present in 11%. Atypical pneumonia was identified in 27% of the azithromycin arm cases. Data on *S. pneumoniae* eradication rates and clinical response, according to bacterial susceptibility to macrolides and penicillin, were analyzed in both studies (Tables 4 and 5). No clear relationship between resistance patterns and clinical and bacteriological outcomes was observed. In the two studies combined, 13 azithromycin-resistant *S. pneumoniae* strains were found, 7 of which were treated with azithromycin, with clinical cure and bacteriological eradication (presumed or documented) being obtained in 4/7.

Macrolide-resistant pneumococci are increasing worldwide (Gay et al 2000). However, the clinical significance of this finding is still debated as resistance has been associated with clinical failure in some (Fogarty et al 2000) but not all studies (Aspa et al 2004). Particularly, treatment failure is not unusual in cases of bacteremic pneumococcal pneumonia (Lonks 2002), although most clinical failures showed underlying conditions that would have contraindicated the empirical choice of a macrolide as first line treatment. As mentioned above, the administration of a single high dose of azithromycin is likely to result in concentrations of azithromycin in lung tissue and fluids that would be effective against *S. pneumoniae* with low-level macrolide resistance.

The safety and tolerability of this novel azithromycin formulation were excellent. The majority of all reported adverse events were mild or moderate in severity. For azithromycin microspheres, most adverse events occurred on the day of administration and resolved within 2 days. There were no clinically significant changes in clinical laboratory

Table 2 Demographics and baseline characteristics of patients included in two comparative phase III community-acquired pneumonia studies of 2 g single-dose azithromycin microspheres (D'Ignazio et al 2005; Drehobl et al 2005)

	Drehobl et al 2005		D'Ignazio et al 2005	
	Azithromycin microspheres (n = 247)	Clarithromycin XL 1.0 g (n = 252)	Azithromycin microspheres (n = 211)	Levofloxacin 500 mg (n = 212)
Mean age (years)	45.6	43.6	48.2	49.0
No. of subjects ≥65 years (%)	32 (13%)	26 (10.3%)	49 (23.2%)	48 (22.6%)
Male/female	112/135	134/118	121/90	109/103
History of diabetes	13	11	20	27
Unilobar disease	211	219	172	181
Smoker/ex-smoker	131	139	99	100

Abbreviation: XL, extended release.

Table 3 Clinical and bacteriological response rates at days 14-21 in two studies comparing azithromycin 2.0 g microspheres with either extended release clarithromycin or levofloxacin in patients with community-acquired pneumonia (D'Ignazio et al 2005; Drehobl et al 2005)

	Drehobl et al 2005		D'Ignazio et al 2005	
	Azithromycin microspheres	Clarithromycin XL 1.0 g	Azithromycin microspheres	Levofloxacin 500 mg
Clinical response	92.6% (n = 202)	94.7% (n = 209)	89.7% (n = 174)	93.7% (n = 209)
Bacteriological response	93.0% (n = 100)	92.1 (n = 127)	90.1% (n = 91)	92.3% (n = 104)
Clinical response by pathogen				
Haemophilus influenzae	14/15 (93%)	23/26 (88%)	14/15 (93%)	8/8 (100%)
Moraxella catarrhalis	8/8 (100%)	3/5 (60%)	7/7 (100%)	2/2 (100%)
Streptoccoccus pneumoniae	17/19 (89%)	25/27 (93%)	11/14 (79%)	10/12 (83%)
Chlamydia pneumoniae	19/21 (90%)	29/31 (94%)	18/19 (94%)	21/22 (95%)
Mycoplasma pneumoniae	25/26 (96%)	20/21 (95%)	5/7 (71%)	18/18 (100%)

Abbreviation: XL, extended release.

parameters. Table 6 shows the adverse reactions recorded in the two studies. In both studies, the azithromycin group showed a greater number of diarrhea and loose stools adverse events. In most cases the effect was limited to the day of therapy or the following day.

Owing to the single-dose nature of the regimen, all azithromycin-treated patients completed the treatment course, whereas 15 of 254 subjects (5.9%) randomized to the clarithromycin XL arm did not complete the entire 7-day course of active treatment and 10 of the 212 levofloxacin-treated subjects (4.7%) did not complete the full 7-day treatment course.

The results of these controlled trials in CAP demonstrated that a single 2.0 g dose of azithromycin microspheres is at least as effective as a 7-day treatment with either clarithromycin extended release or levofloxacin, confirming the suitability of the new formulation of azithromycin.

Azithromycin microspheres in acute exacerbations of chronic bronchitis

Proper management of an AECB should result in rapid resolution of the acute episode and decrease in the likelihood of treatment failure and of an early recurrence (Martinez 2005). The role of antibiotic treatment in AECB is less straightforward than in CAP. It is felt that only approximately 50% of exacerbations are sustained by bacteria (Monso et al 1995) and the issue is complicated by the fact that approximately 25%–40% of COPD patients present stable bacterial colonization of the airways outside periods of acute deterioration (Cabello et al 1997). Attempts have been made to identify patients more likely to present bacterial aetiology of an exacerbation based on the presence of at least 2 out of 3 of the clinical Anthonisen criteria (increased cough, increased

in sputum production, change in sputum color) (Anthonisen et al 1987). Among the three symptoms, sputum purulence has been most strongly associated with bacterial exacerbation (Stockley et al 2000; Allegra et al 2005). Additionally, patient baseline severity must also be considered as antibiotics have a greater beneficial effect in patients with more severe disease (Allegra et al 2001), which translates into a survival advantage in those sufficiently severe to require mechanical ventilation (Nouira et al 2001). Regrettably, in most older antibiotic efficacy studies on patients with exacerbations a precise definition of COPD was often absent, with enrolment of young, non-obstructed never-smokers, unsatisfactory definitions of exacerbation, high population severity heterogeneity, and lacked stratification for steroid use.

A recent double-blind, double-dummy study compared azithromycin microspheres (2 g single dose) with levofloxacin (500 mg once daily for 7 days) in patients with AECB (Zervos et al 2005). Patients were clearly defined with stratification for the use of systemic steroids, and strict inclusion and exclusion criteria. A total of 551 subjects were randomized and 438 were treated at 62 centers in 13 countries. Most enrolled subjects were advanced-age patients with a past history of smoking, documented airflow

Table 4 Antimicrobial susceptibility of the 56 *Streptococcus pneumioniae* isolates identified in the study comparing azithromycin 2.0 g microspheres with extended release clarithromycin (Drehobl et al 2005)

	Susceptible	Intermediate	Resistant
Penicillin	38 (68%)	16 (29%)	2 (4%)
Azithromycin	49 (88%)	1 (2%)	6[a] (11%)
Clarithromycin	50 (89%)	0	6 (11%)

[a]2/6 among azithromycin-treated patients.

Table 5 Antimicrobial susceptibility of the 28 *Streptococcus pneumioniae* isolates identified in the study comparing azithromycin 2.0 g microspheres with extended release clarithromycin (D'Ignazio et al 2005)

	Susceptible	Intermediate	Resistant
Penicillin	19 (68%)	8 (29%)	1 (4%)
Azithromycin	21 (75%)	0	7[a] (25%)
Levofloxacin	28 (100%)	0	0

[a]5/7 among azithromycin-treated patients.

obstruction, at least one AECB in the previous year, and presented all three cardinal Anthonisen symptoms in the current exacerbation. Patient baseline demographic characteristics are shown in Table 7.

The clinical cure rate at the test-of-cure (TOC) visit (Days 14–21) in the treated population was comparable between the two agents (93.6% for azithromycin compared with 92.7% for levofloxacin). Baseline microbiological testing yielded positive results in approximately 49% of subjects. In these patients, the overall bacteriological eradication rate was comparable between the two treatment regimens (91.9% for azithromycin versus 94.4% for levofloxacin).

Additional post hoc analyses of the 272 subjects in this study with spirometric evidence of airway obstruction suggests equal efficacy of azithromycin microspheres compared with levofloxacin across all strata of COPD severity using the GOLD and ATS/ERS stratification schemes (Pauwels et al 2001; Celli et al 2004) (Table 8). The majority of enrolled patients presented advanced disease severity. During the course of the trial and the follow-up period, 12 patients needed hospitalization. Eight of these occurred in the levofloxacin-treated arm while 4 occurred in azithromycin microsphere-treated patients. There was no clear pattern noted, although the majority of hospitalized patients had more severe airway obstruction at baseline.

Among the patients treated with azithromycin microspheres, 5 were found to harbor macrolide-resistant *S. pneumoniae* strains. All patients were reported as clinically cured. In 1 patient with the highest macrolide MIC values (>256 μg/mL), persistence of the baseline pathogen was established at the 10-day TOC visit despite clinical resolution of the acute symptoms.

Conclusions

Optimal duration for antimicrobial treatment in lower respiratory tract infections (LRTIs) is still undetermined. Short-course treatments may be a means for maintaining clinical efficacy while containing antibiotic resistance spread, increasing patient compliance, and limiting drug-related adverse events. As recently pointed out by Thomas M. File (File 2004), the basic rationale behind short-course antibiotic treatment in CAP is to "hit hard and stop early". Candidate drugs must show favorable pharmacokinetic and pharmacodynamic properties allowing high and prolonged antimicrobial concentrations at the site of infection.

The novel azithromycin microsphere formulation takes the concept of short-course treatment one step further by allowing single-dose antibiotic administration in LRTIs. Use of this formulation allows greater peak concentrations of the drug early in the course of infection with similar overall total antimicrobial exposure compared to traditional 3- to 5-day dosing regimens. This may allow sufficiently high concentration to effectively eradicate even moderately resistant organisms. The results of controlled trials in CAP and COPD exacerbations demonstrate that a single dose of azithromycin microspheres is at least as effective and well tolerated as a 7-day treatment with either extended release clarithromycin or levofloxacin.

An undoubted advantage of single-dose azithromycin administration is the facility in ensuring that patients complete their prescribed course of therapy. Failure to complete

Table 6 Incidence of adverse events in two studies comparing azithromycin 2.0 g microspheres with either extended release clarithromycin or levofloxacin in patients with community-acquired pneumonia (D'Ignazio et al 2005; Drehobl et al 2005)

	Drehobl et al 2005		D'Ignazio et al 2005	
	Azithromycin microspheres (n = 247)	Clarithromycin XL 1.0 g (n = 252)	Azithromycin microspheres (n = 211)	Levofloxacin 500 mg (n = 212)
Diarrhea/loose stools	30 (12.1%)	19 (7.5%)	27 (12.8%)	11 (5.2%)
Nausea	9 (3.6%)	8 (3.2%)	3 (1.4%)	2 (0.9%)
Abdominal pain	9 (3.6%)	3 (1.2%)	4 (1.9%)	2 (0.9%)
Rash	3 (1.2%)	1 (0.4%)	1 (0.5%)	0
Taste perversion	3 (1.2%)	9 (3.6%)	0	1 (0.5%)
Vomiting	2 (0.8%)	2 (0.8%)	4 (1.9%)	2 (0.9%)

Abbreviation: XL, extended release.

Table 7 Patient baseline demographics in a study comparing azithromycin 2.0 g microspheres with levofloxacin 500 mg in acute exacerbations of chronic bronchitis (Zervos et al 2005)

Characteristic	Azithromycin microspheres (n = 268)	Levofloxacin 500 mg (n = 2742)
Mean age (years)	62.3	61.7
Systemic steroids	27 (10.1%)	27 (9.9%)
FEV$_1$ % predicted		
>80	44 (16.4%)	35 (12.8%)
<80 and >60	50 (18.7%)	57 (20.8%)
<60 and >30	111 (41.4%)	110 (40.1%)
<30	31 (11.6%)	38 (13.9%)
Missing	32 (11.9%)	34 (12.4%)
Smoking history		
Smoker	156 (58.2%)	163 (59.5%)
Ex-smoker	109 (40.7%)	111 (40.5%)
Never-smoker	3 (1.1%)	0 (0%)
Anthonisen criteria		
Presence of all three criteria	263 (98.1%)	269 (98.2%)
Presence of two criteria	5 (1.9%)	4 (1.5%)
Presence of one criterion	0 (0%)	1 (0.4%)
No. AECB in the previous year		
1–4	213 (79.5%)	218 (79.6%)
>4	21 (7.8%)	21 (7.7%)
None	34 (12.7%)	34 (12.4%)

Abbreviations: AECB, acute exacerbations of chronic bronchitis; FEV$_1$, forced expiratory volume in 1 second; Anthonisen criteria: increased cough, increased in sputum production, change in sputum color.

therapy may be associated with deterioration in the patient's condition, treatment failure, and increased use and cost of healthcare resources such as the requirement for additional drugs and hospital admission. Incomplete treatment may also increase the likelihood that bacteria will develop resistance. Another advantage of single-dose therapy is the potential for use as directly observed therapy (DOT). The use of a DOT in LRTIs is intriguing, particularly in congested clinical situations (such as emergency departments) where assuring

Table 8 Subset analysis of favourable clinical response rates (expressed as percentage) of azithromycin 2.0 g microspheres or levofloxacin 500 mg in 272 AECB patients with differing degrees of airway obstruction (Zervos et al 2005)

	Azithromycin microspheres (n = 136)	Levofloxacin 500 mg (n = 136)
Degree of airway obstruction		
Mild	88.9%	100%
Moderate	95.7%	94.1%
Severe	94.4%	92
Very severe	88.5%	89.7%

patient compliance may be troublesome or barriers to filling prescriptions may exist.

Predictably, such a form of treatment may encounter some resistance among interested parties. Physicians may be doubtful as to whether a single dose regimen may be reliable and effective for the treatment of their patients with LRTIs. Similarly, patients are accustomed to taking medications everyday while they are sick, with interruption of treatment often coinciding with symptom resolution. Clearly, further sound clinical demonstration of efficacy and recognition of patient subsets most likely to benefit are needed before widespread use of this approach to LRTIs can be considered.

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