REVIEW

Legionella: macrolides or quinolones?

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ABSTRACT

Following the first outbreaks of legionnaire's disease, erythromycin emerged as the treatment of choice without the foundation of rigorous clinical trials. The number of therapeutic failures with erythromycin, as well as the side-effects and drug interactions, led to the consideration of other drugs such as the new macrolides and quinolones for the treatment of legionnaire's disease in the 1990s. In this article, 19 studies in in-vitro intracellular models and seven animal studies that compared macrolides to quinolones were reviewed. Quinolones were found to have greater activity in intracellular models and improved efficacy in animal models compared with macrolides. No randomised trials comparing the clinical efficacy of the new macrolides and new quinolones have ever been performed. Three observational studies totalling 458 patients with legionnaire's disease have compared the clinical efficacy of macrolides (not including azithromycin) and quinolones (mainly levofloxacin). The results suggested that quinolones may produce a superior clinical response compared with the macrolides (erythromycin and clarithromycin) with regard to defervescence, complications, and length of hospital stay. Little data exist for direct comparison of quinolones and azithromycin.

Keywords azithromycin, clarithromycin, legionella, levofloxacin, macrolides, quinolones, review

INTRODUCTION

Controlled trials of antibiotics for the treatment of legionnaire's disease have never been conducted for a number of reasons. In the American Legion outbreak of 1976, patients treated with erythromycin and tetracycline fared better than those treated with other antibiotics (especially β-lactam antibiotics) [1]. Subsequent experience with hospital-acquired legionnaire's disease also suggested the superiority of erythromycin over other antibiotics [2,3]. Thus, erythromycin emerged as the drug of choice based on anecdotal experience [4].

On the other hand, treatment failures with erythromycin [5–7] led to the empirical practice of increasing the dose of erythromycin (from 500 mg to 1 gram four times a day) and the addition of rifampin; no data were ever generated to support this practice which soon became commonplace. Its interaction with the metabolism of numerous drugs, as well as the adverse effects of fluid overload and ototoxicity because of high doses, also became problematic. In the 1990s the newer macrolides (azithromycin, clarithromycin, roxithromycin) and quinolones were introduced, with notably greater in-vitro activity than erythromycin. Quinolones were shown to be more active than any macrolides for *Legionella* in in-vitro studies, intracellular models, and animal models, but it was unclear whether this superiority would be translated into clinical practice.

The intracellular location of the pathogen proved to be relevant to the efficacy of the antibiotic. Specifically, antibiotics capable of achieving intracellular concentrations higher than the MIC were more clinically effective than antibiotics with poor intracellular penetration [8]. For example, erythromycin and rifampin were able to prevent death in guinea pigs inoculated intraperitoneally with large numbers of *Legionella*. On the other hand, antibiotics with poor intracellular presentation (penicillin,

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chloramphenicol, tetracycline, and gentamicin) were ineffective in preventing death [9,10]. Thus, the theoretical basis for the empirical observation that macrolides, quinolones, tetracyclines, and rifampin were more likely to be efficacious was supported by a biological rationale since these antibiotics achieved relatively high intracellular penetration.

The recommendation of the use of macrolides such as azithromycin as preferred therapy was introduced in the first North American consensus guidelines for empirical therapy of patients with community-acquired pneumonia [11–13]. Quinolones also became widely used for community-acquired pneumonia because of their activity against *Legionella pneumophila* and the spectre of penicillin-resistant pneumococci [14] (a fear which is now known to be unjustified).

SUSCEPTIBILITY TESTING

Dilutional tests of in-vitro susceptibility in agar or broth have correlated poorly with clinical outcome since they measure extracellular susceptibility. Thus, intracellular models and animal studies have supplanted the standard tests for antimicrobial susceptibility testing. In 19 studies in in-vitro intracellular models of *Legionella* susceptibility, quinolones were consistently more active than macrolides (Table 1). Likewise, in seven comparative studies performed in animal models, quinolones were superior to macrolides (Table 2).

COMPARATIVE CLINICAL STUDIES

Comparative antibiotic studies have not been performed because, in the early years following discovery of legionnaire's disease, patients were identified mainly in outbreaks, making it difficult to perform a controlled trial. Patients with hospital-acquired legionnaire's disease were not studied because disinfection of the drinking water reservoir was ethically required upon discovery of cases; following disinfection, subsequent cases were unlikely to occur. Nevertheless, three observational studies have addressed the comparative efficacy of quinolones and macrolides.

Blazquez *et al.* [15] conducted an observational, prospective study of 292 patients with *L. pneumonia* during the Murcia, Spain outbreak. Patients were stratified according to the severity of pneumonia in order to compare those who received macrolides (*n* = 65) and those who received levofloxacin (*n* = 143). Mykietiuk *et al.* [16] conducted a prospective, observational series of 1934 consecutive cases of community-acquired pneumonia in non-immunocompromised adults [16]. One hundred and thirty-nine cases of legionnaire's disease were diagnosed. Patients were classified into two groups based on therapy: macrolides (*n* = 80) or levofloxacin (*n* = 40) therapy. Sabria *et al.* [17] conducted a retrospective observational multicentre study of legionnaire's disease that included 76 patients who received macrolides and 54 patients who received fluoroquinolones (50 levofloxacin and four ofloxacin).

When the results of all studies were combined: 51.2% (128/250) were smokers [16,17]; 23.6% (59/250) had chronic pulmonary diseases [16,17]; 44.1% (202/458) had no underlying diseases; 6.9% (32/458) required ICU admission [15–17]. No significant differences were found among the three studies concerning age, sex, cigarette smoking, chronic lung diseases, and severity of pneumonia for the two treatment groups (macrolides and quinolones). Unlike the studies of Garrido and Mykietiuk, immunosuppressed patients (13%) and cases of hospital-acquired legionnaire's disease (17.6%) were included in the multicentre study by Sabrià *et al.* [17]. Forty-five per cent (205/458) were diagnosed according to antibody seroconversion [15,16], 85.1% (390/458) according to urinary antigen test positivity for *L. pneumophila* serogroup 1 [15–17], and 9.3% (43/458) according to isolation from culture [16].

Time to defervescence was notably shorter in patients receiving levofloxacin in two studies [16,17]. The mean time was 97.7 h for patients receiving macrolides and 66.6 h for those receiving levofloxacin in the three studies. Length of hospital stay was significantly shorter for patients treated with levofloxacin in all three studies. The mean hospital stay for all three studies was 9.0 days for patients receiving macrolides and 6.6 days for the levofloxacin group. Patients receiving levofloxacin had fewer complications (8.4%, 20/237), as defined by pleural effusion, empyema, cavitation, septic shock, and mechanical ventilation, than those receiving macrolides (18.5%, 41/221) [15–17].

The incidence of treatment-related adverse events was 23.4% (34/145) for patients receiving macrolides and 12.5% (23/183) for those receiving

Table 1. Activity of quinolones vs. macrolides in intracellular models

References	Cellular Model	*Legionella* sp./ serogroups	Comparative activity	Comment
Fitzgeorge,1985 [27]	Guinea pig pulmonary alveolar macrophages	Lp	Levo > Ery	
Havlichek, 1987 [28]	Human monocytes	Lp serogroup 1	Cipro > Amflo > Cino> Enox > Roso > Ery	
Fitzgeorge, 1988 [29]	Guinea pig pulmonary alveolar macrophages	Lp serogroup 1	Oflox > Cipro > Ery	
Edelstein, 1989 [30]	Guinea pig pulmonary alveolar macrophages	L.spp.	WIN57273, Cipro and Ery all inhibited growth of Lp at concentrations of 1 mg/L, but only WIN 57273 prevented regrowth or killed Lp after removal of extracellular antimicrobial agent.	
Edelstein, 1991 [31]	Guinea pig pulmonary alveolar macrophages	Lp	Azi and Cipro were both bactericidal but Ery was bacteriostatic	
Kitsukawa, 1991 [32]	Guinea pig pulmonary alveolar macrophages	Lp	AT-4140 > Roxi > Oflo = Cipro > Ery	
Edelstein, 1996 [33]	Guinea pig pulmonary alveolar macrophages	Lp serogroup 1,4,6,9; L. dumoffii serogroup 1, L. micdadei, L. longbeachae, L. bozemanii serogroup 2	1) Levo showed similar activity to Oflox (2) Levo was slightly less active than Cipro (3) Levo and Oflox were more active than Ery	Levo and Oflox showed a more prolonged PAE than Ery
Walz, 1997 [34]	J774 macrophage	Lp	BAY Y 3118 and Clina > Cipro > Ery	
Smith, 1997 [35]	Human mononuclear phagocytes	L.p serogroup 1	Levo and Ery produced effective inhibition on Lp. The delay of regrowth with Ery was < 30 min The delay of regrowth with Levo was > 72 h	
Baltch, 1998 [36]	Human monocytes	Lp serogroup 1	Levo > Ery	After removal of Levo from human monocytes, the continued suppression of Lp was greater than that for Ery
Stout, 1998 [37]	HL-60 cell line	Lp, serogroups 1,2,3,4,5,6; L. micdadei, L. bozemanii, serogroup 1, L. jordanis	Levo > Cipro > Oflox > Ery	All quinolones were more potent against. L. micdadei and L. bozemanii when compared to Lp
Stout, 1998 [38]	HL-60	Lp, serogroup 1, L. micdadei, L. bozemanii	Azi > Clari > Roxitho > Quinupristin/dalfo > Ery > Diritho	
Edelstein, 1999 [39]	Guinea pig pulmonary alveolar macrophages	LP serogroup 1	Levo > Clari = Ery	Clarithro and Ery were bacteriostatic Levo was bactericidal
Edelstein, 2001 [40]	Guinea pig pulmonary alveolar macrophages	Lp	Levo = Gemi = Azithro and > Ery	Ery was bacteriostatic. Levo, Gemi and Azithro were bactericidal
Baltch, 2005 [41]	derived macrophages	Human monocyte	Lp, L. micdadei L. micdadei: Gemi > Q (Levo, Gati, Moxi) > Ery Lp: Moxi > Q (Gemi, Levo, Gati) > Ery	
Baltch, 2005 [41]	Human monocytes	Lp serogroup 1, L. micdadei	Gemi, Levo, Gati and moxi had similar activities against Lp and L. micdadei at 10x and > Ery	At 24 h, Moxi > Gemi, Levo, Gati against Lp, while Gemi > than the other quinolones against L. micdadei. The PAE of Gemi against Lp was dose dependent
Stout, 2005 [42]		HL-60 L. micdadei, L. dumoffii, L. longbeachae, L. feeleii L. bozmanii	Lp, serogroups 1–15 1) Q > Ketolides > M (2) Levo > Moxi > Gemi > Grepa > Cipro > Trova > Ery (3) Ketolides > Azi > Clari > Ery	
Stout, 2005 [42]	HL-60 cell line	Lp serogroup 1	Azithro > Ery Levo > Moxi > Gemi > Grepa > Cipro > Trova > Ery	
Tano, 2005 [43]	HEp-2 cells Glass chamber	Lp serogroup 1	Moxi > Ery	

Lp, *Legionella pneumophila*; Azi, Azithromycin; Clari , Clarithromycin; Roxi, Roxithromycin; Ery, Erythromycin; Levo, Levofloxacin; Moxi, Moxifloxacin; Cipro, Ciprofloxacin; Clina, Clinafloxacin; Grepa, Grepafloxacin; Gemi, Gemifloxacin; Oflox, Ofloxacin; Trova, Trovafloxacin; Amflo, Amifloxacin; Enox, Enoxacin; Cino, Cinoxacin; Roso, Rosoxacin; M, Macrolides; Q, Quinolones; PAE, Post antibiotic effect.

levofloxacin. Phlebitis was the most frequent adverse effect, but none of the affected patients had to discontinue the antibiotic.

The delay until the initiation of an appropriate antibiotic treatment was only noted in the Sabrià study and was not significantly different in the two groups (78.5 h for the macrolide group vs. 92.7 h for the quinolone group). The time in which intravenous administration of antibiotics was switched to oral therapy was significantly shorter in the quinolone group (3.8 days in the quinolone group vs. 5.3 days in the macrolide group) [16,17].

The overall mortality was 4.5% (10/221) for the macrolide group and 2.1% (5/237) for the levofl-oxacin group. In summary, the results from these three observational studies [15–17], totalling 458 patients with legionnaire's disease, suggested that levofloxacin may produce a superior clinical response compared with macrolides for end-points of defervescence and hospital stay (Table 3); however, the mortality rate was similar.

Limitations

As mentioned, none of the above studies were randomised trials, so biases could easily have been present. Multiple subgroup analysis was suggested as a flaw in the statistical analysis of

Table 2. Activity of macrolides compared with quinolones in animal models

				Outcome Survival	
Reference	Antimicrobial Agents	*Legionella*	Animal/Model	Macrolide	Quinolone
Saito, 1986 [44]	Ery vs. Cipro	Lp	Guinea pig	60%	80%
Saito, 1985 [45]	Ery, Josa vs. Oflox	Lp	Guinea pig	Ery 60%, Josa 0%	80%
Edelstein, 2001 [46]	Azithro vs. Gemi, Levo	Lp	Guinea pig	100%	Gemi 100%, Levo 100%
GarcíadeLomas, 1998 [47]	Ery vs. Trova	Lp	Guinea pig	90%	100%
Dormon, 1986 [48]	Ery vs. Peflo	Lp	Guinea pig	Mortality was significantly lower for quinolones	
Edelstein, 1990 [49]	Ery vs. Spar	Lp	Guinea pig	No differences in mortality but lung cultures from survivors were significantly more frequently positive for Lp in the Ery-treated animals	
Tzianabos, 1989 [50]	Ery vs. Cipro	Lp, serogroup 1	Hen's eggs	Quinolones were more effective in reducing the incidence of lesions and for prolonging embryo viability	

Azithro, Azithromycin; Levo, Levofloxacin; Cipro, Ciprofloxacin; Oflox, Ofloxacin; Ery, Erythromycin; Peflo, Pefloxacin; Gemi, Gemifloxacin; Spar, Sparfloxacin; Josa, Josamycin; Trova, Trovafloxacin.

Table 3. Clinical response of macrolides compared with quinolones in three observational studies

	Patients (n)		Time Defervescence (h)		Hospital stay (days)		Complications		Mortality		Adverse Effects	
Study	M	Q	M	Q	M	Q	M	Q	M	Q	M	Q
Sabrià, 2005 [17]	76	54	77.1	48	9.9	7.6	23.6% (18/76)	16.6% (9/54)	7.8% (6/76)	5.5% (3/54)	NA	NA
Mykietiuk, 2005 [16]	80	40	108	48	10	8	25% (20/80)	25% (10/40)	5% (4/80)	2.5% (1/40)	30% (24/80)	20% (8/40)
Blázquez, 2005 [15]	65	143	108	104	7.2	4.4	4.6% (3/65)	0.6% (1/143)	0% (0/65)	0.6% (1/143)	15.3% (10/65)	10.4% (15/143)
Total	221	237	97.7	66.6	9.03	6.6	18.5% (41/221)	8.4% (20/237)	4.5% (10/221)	2.1% (5/237)	23.4% (34/145)	12.5% (23/183)

NA, not available; n, number of patients; M, macrolides; Q, quinolones.

the Blazquez study [19], although we agree with the authors of the study that the endpoints of outcome showed a consistent trend toward the superiority of levofloxacin. Forty-eight patients in the macrolide group in the Mykietiuk study also received rifampicin but these patients were not analysed separately, although it would seem that this inclusion should not lead to a bias against macrolides. The doses of quinolones used in the three studies were not controlled. The starting doses of levofloacin until defervescence were higher (500 mg every 12 h) in the Sabrià study than the standard doses usually recommended (500 mg once a day). Treatment failures using low doses of ofloxacin [20] or ciprofloxacin [21,22] in legionnaire's disease have been described.

A more severe limitation, in our opinion, was that the title of each of the three articles used the encompassing term 'macrolides'. Clarithromycin was the predominant macrolide used in treating the patients with severe pneumonia in the Blazquez study, clarithromycin and erythromycin in the Mykietiuk study, and erythromycin in the Sabrià study. Azithromycin was not included in any systematic comparison; this is pertinent in that numerous studies have shown that azithro-

mycin is more active than clarithromycin and erythromycin in intracellular models (Table 1). And, in one intracellular model [40] and one animal study [46], azithromycin was comparable to the quinolones tested. So, the issue of the superiority of quinolones over azithromycin has not been directly addressed.

A surprising 0% mortality was the case for 75 patients receiving levofloxacin for legionnaire's disease in six clinical trials performed for the US Food and Drug Administration (FDA) approval of levofloxacin [18]. This was the largest antibiotic study ever published of patients with community-acquired pneumonia in which legionnaire's disease was identified; not a single death was recorded.

CONCLUSIONS

The advantages of choosing a quinolone over a macrolide for treatment of legionnaire's disease in immunocompetent patients with community-acquired pneumonia may be a shorter time to defervescence with a more rapid achievement of clinical stability, followed by shorter hospital stay. Reduction in hospital stay of only 1 day can reduce healthcare costs by a notable amount.

Until definitive studies are performed, how should the clinician manage patients? Based on data from intracellular susceptibility tests, animal studies and observational studies, we suggest that quinolones might warrant preference over macrolides in compromised hosts with severe infections who are critically ill. Respiratory failure, hospital-acquisition, advanced cancer, immunosuppressive chemotherapy and HIV infection are poor prognostic factors for legionnaire's disease; mortality rates in these subsets of patients are notably higher (> 20%) [23–26]. In these cases, a more aggressive therapeutic approach might be prudent so as to maximize outcome.

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