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Antipneumococcal Activity of LBM415, a New Peptide Diformylase Inhibitor, Compared with Those of Other Agents

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The MICs of LBM415, a new peptide diformylase inhibitor, were evaluated and ranged from 0.03 to 4.0 μg/ml for 300 pneumococci, irrespective of their β-lactam, macrolide, and quinolone susceptibilities. By comparison, vancomycin, teicoplanin, linezolid, and quinupristin-dalfopristin were also active, with MICs ≤2.0 μg/ml. Gatifloxacin and moxifloxacin were the most active quinolones tested, while the MICs of the β-lactams rose with those of penicillin G. LBM415 at two times the MIC was bactericidal (99.9% killing) against six strains after 24 h.

The incidence of pneumococci resistant to penicillin G and other β-lactams and non-β-lactams has increased worldwide, including the United States, at an alarming rate (3, 6, 10, 11). The higher the penicillin G MIC is, the more likely it is that pneumococci will also be resistant to macrolides and other unrelated agents (11). The recent emergence of quinolone-resistant pneumococci (15) has further complicated the therapeutic problem. There is an urgent need for oral compounds for the outpatient treatment of respiratory tract infections caused by resistant pneumococci (6).

LBM415 (previously known as NVP-PDF713) is a new peptide deformylase inhibitor with excellent activities against gram-positive bacteria (1, 2, 7, 12, 13). The present study examined (i) the antipneumococcal activities of LBM415 compared with those of penicillin G, amoxicillin, amoxicillin-clavulanate, imipenem, meropenem, ceftriaxone, cefuroxime, cefpodoxime, cefdinir, ciprofloxacin, levofloxacin, gatifloxacin, moxifloxacin, azithromycin, clarithromycin, linezolid, quinupristin-dalfopristin, vancomycin, and teicoplanin against 300 pneumococci by the agar dilution MIC methodology and (ii) the activities of the compounds listed above plus daptomycin against 12 pneumococci by time-kill analysis.

The pneumococci used for the agar dilution studies comprised 80 penicillin-susceptible, 88 penicillin-intermediate, and 132 penicillin-resistant strains. Of these, 154 were macrolide resistant and had the following mechanisms of resistance: *erm*(B), 87 isolates; *mef*(A), 40 isolates; *erm*(B) and *mef*(A), 1 isolate; L4 protein mutation, 18 isolates; 23S rRNA mutation, 4 isolates; and *erm*(A), 4 isolates. Forty-two penicillin-susceptible but macrolide-resistant strains were chosen for this study. Thirty strains were quinolone resistant (levofloxacin MICs, ≥4 μg/ml) and had defined mutations in the type II topoisomerase enzymes. Twelve pneumococcal strains were tested in the time-kill studies: four penicillin-sensitive strains, two intermediate strains, and six penicillin-resistant strains. Of these 12 strains, 10 were macrolide resistant [4 had *erm*(B), 4 had *mef*(A), and 2 had an L4 protein mutation] and 2 were quinolone resistant. LBM415 powder for susceptibility testing was obtained from Novartis Research Laboratories, Hanover, N.J. The other antimicrobials were obtained from their respective manufacturers. The agar dilution method was performed with Mueller-Hinton agar (BBL Microbiology Systems, Cockeysville, Md.) supplemented with 5% sheep blood. Although NCCLS recommends use of the microdilution method to determine MICs for pneumococci, our group has successfully performed the agar dilution method for many years, with uniformly satisfactory quality control and other results (3, 10, 19, 21, 22). All compounds except daptomycin were tested by the agar dilution method. Daptomycin may not be tested by this method because of problems with calcium regulation in agar (20). The MICs for the 12 strains determined by the time-kill method were confirmed by the standard macrodilution method (17). Standard quality control strains were included in each run (17).

For the time-kill studies, tubes containing 5 ml of cation-adjusted Mueller-Hinton broth (BBL Microbiology Systems) with 5% lysed horse blood and doubling antibiotic concentrations were inoculated with 5×10^5 to 5×10^6 CFU/ml, and the tubes were incubated at 35°C in a shaking water bath. The methods were those described previously (18, 24, 25), with the addition of calcium for the studies with daptomycin.

The results of the time-kill assays were analyzed by determining the number of strains which yielded changes in the $\log_{10}$ CFU per milliliter of −1, −2, and −3 at 0, 3, 6, 12, and 24 h compared to the counts at time zero. The lowest concentration of an antimicrobial that reduced the original inoculum by ≥3 $\log_{10}$ CFU/ml (99.9%) at each of the time periods was considered bactericidal, and the lowest concentration of an antimicrobial that reduced the original inoculum by 0 to <3 $\log_{10}$ CFU/ml was considered bacteriostatic. The problem of antibiotic carryover was addressed by dilution, as described previously (18, 24, 25). Ten strains for which ciprofloxacin MICs were <8.0 μg/ml were used to test the quinolones by the time-kill method. Only two strains for which erythromycin MICs were 0.03 μg/ml were used in tests with azithromycin and clarithromycin by the time-kill method.

The MICs for the 300 strains classified by their penicillin susceptibilities are summarized in Table 1, and the MICs for

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TABLE 1. Agar dilution MICs for 300 strains classified by penicillin susceptibility

Drug and penicillin susceptibility[a]	MIC (μg/ml)			Drug and penicillin susceptibility[a]	MIC (μg/ml)		
	Range	50%	90%		Range	50%	90
Penicillin				Ciprofloxacin			
S	0.016–0.06	0.03	0.06	S	1.0–>32.0	2.0	32.0
I	0.125–1.0	0.25	1.0	I	0.5–32.0	1.0	2.0
R	2.0–16.0	2.0	4.0	R	0.5–>32.0	2.0	4.0
LBM415				Levofloxacin			
S	0.06–4.0	1.0	2.0	S	1.0–32.0	1.0	16.0
I	0.03–2.0	0.5	1.0	I	0.5–32.0	1.0	2.0
R	0.06–4.0	0.5	1.0	R	0.5–32.0	1.0	2.0
Amoxicillin				Gatifloxacin			
S	≤0.016–0.125	0.03	0.03	S	0.25–8.0	0.5	4.0
I	≤0.016–2.0	0.25	1.0	I	0.125–16.0	0.25	0.5
R	0.25–16.0	2.0	8.0	R	0.125–16.0	0.5	1.0
Amoxicillin-clavulanate				Moxifloxacin			
Penicillin S	≤0.016–0.125	0.03	0.03	S	0.125–4.0	0.25	4.0
Penicillin I	0.03–2.0	0.25	1.0	I	0.06–4.0	0.125	0.25
Penicillin R	0.25–16.0	2.0	4.0	R	0.06–4.0	0.25	0.5
Imipenem				Azithromycin			
S	≤0.004–0.03	0.008	0.008	S	0.03–>64.0	2.0	>64.0
I	0.016–0.25	0.03	0.125	I	≤0.016–>64.0	2.0	>64.0
R	0.06–2.0	0.25	0.25	R	0.06–>64.0	0.125	>64.0
Meropenem				Clarithromycin			
S	0.008–0.06	0.016	0.016	S	≤0.016–>64.0	0.5	>64.0
I	0.016–0.5	0.06	0.25	I	≤0.016–>64.0	1.0	>64.0
R	0.125–2.0	0.5	0.5	R	≤0.016–>64.0	0.06	>64.0
Ceftriaxone				Cefpodoxime			
S	0.008–0.25	0.03	0.06	S	0.03–0.5	0.03	0.06
I	0.03–1.0	0.125	1.0	I	0.06–4.0	0.25	2.0
R	0.5–>8.0	1.0	2.0	R	1.0–64.0	4.0	8.0
Cefuroxime				Cefdinir			
S	0.016–0.5	0.03	0.125	S	0.016–0.5	0.06	0.125
I	0.125–4.0	0.25	4.0	I	0.06–8.0	0.5	4.0
R	2.0–64.0	4.0	16.0	R	2.0–>64.0	8.0	8.0

[a] S, susceptible (n = 80); I, intermediate (n = 88); R, resistant. (n = 132).

the 300 strains classified by their macrolide susceptibilities are summarized in Table 2. The LBM415 MICs (range, 0.03 to 4.0 μg/ml; MICs at which 50% of isolates are inhibited [MIC_{50}s], 0.5 to 1.0 μg/ml; MIC_{90}s, 1.0 to 2.0 μg/ml) were similar, irrespective of the strain's β-lactam, macrolide, or quinolone resistance phenotype and genotype. All strains were also susceptible to vancomycin (MICs, 0.03 to 1.0 μg/ml), teicoplanin (MICs, ≤0.016 to 0.125 μg/ml), linezolid (MICs, 0.25 to 2.0 μg/ml), and quinupristin-dalfopristin (MICs, 0.125 to 1.0 μg/ml). The MICs of the β-lactams rose with those of penicillin G. Among the quinolones, moxifloxacin had the lowest MICs for quinolone-susceptible and -resistant strains. The penicillin MICs for macrolide-resistant strains were also generally increased. Because the MICs of the glycopeptides, linezolid, and quinupristin-dalfopristin were similar irrespective of the phenotypic penicillin G and macrolide resistance data, they are not presented in Tables 1 and 2. The quinolone MICs are listed in 1 to reflect their distributions by penicillin G susceptibility.

The MICs for the strains tested by the time-kill method are listed in Table 3, and the results obtained by the time-kill method are listed in Table 4. LBM415 had killing kinetics similar to those of linezolid; at two times the MIC, it was bactericidal (99.9% killing) against six strains after 24 h. The β-lactams, quinolones, and glycopeptides were bactericidal against 12, 9 to 10, and 11 to 12 strains, respectively, at four times the MIC after 24 h. Macrolides showed slower killing. More rapid bactericidal activity, with significant killing at earlier time periods, was seen with daptomycin and quinupristin-dalfopristin.

LBM415 is a new peptide deformylase inhibitor (1, 2, 7, 12, 13) with excellent activity against clinically significant gram-positive strains, including multiresistant organisms such as linezolid-resistant staphylococci (MIC range, 0.25 to 2 μg/ml), *Enterococcus faecalis* (MIC range, 2 to 4 μg/ml), and *Enterococcus faecium*, including strains resistant to quinupristin-dalfopristin (MIC range, 0.5 to 4 μg/ml) (13). In another recent study of 1,837 recent gram-positive strains, the LBM415 MICs for all strains except 6 enterococci (0.3% of strains overall) were ≤4 μg/ml; the MICs for pneumococci ranged from 0.5 to 2 μg/ml (12). A previously published study testing another related peptide

TABLE 2. Agar dilution MICs for 300 strains classified by macrolide susceptibility MIC (μg/ml)

Drug, macrolide susceptibility,[a] and resistance mechanism	MIC (μg/ml)		
	Range	50%	90%
Penicillin			
S	0.016–4.0	1.0	2.0
R	0.016–16.0	0.5	4.0
erm(B)	0.016–16.0	1.0	4.0
mef(A)	0.016–8.0	0.06	2.0
erm(A)	0.016–0.03		
erm(B) + *mef*(A)	0.016		
L4	2.0–16.0	4.0	8.0
23S rRNA	0.03–0.25		
LBM415			
S	0.03–4.0	0.5	1.0
R	0.03–4.0	0.5	2.0
erm(B)	0.06–4.0	0.5	1.0
mef(A)	0.03–4.0	0.25	2.0
erm(A)	1.0–2.0		
erm(B) + *mef*(A)	1.0		
L4	0.125–4.0	0.5	2.0
23S rRNA	0.25–2.0		
Amoxicillin			
S	≤0.016–4.0	1.0	2.0
R	≤0.016–16.0	0.25	8.0
erm(B)	≤0.016–16.0	1.0	8.0
mef(A)	≤0.016–4.0	0.06	2.0
erm(A)	≤0.016–0.03		
erm(B) + *mef*(A)	0.03		
L4	0.25–16.0	4.0	8.0
23S rRNA	0.03		
Amoxicillin-clavulanate			
S	≤0.016–4.0	1.0	2.0
R	≤0.016–16.0	0.25	4.0
erm(B)	≤0.016–16.0	1.0	4.0
mef(A)	≤0.016–4.0	0.06	2.0
erm(A)	≤0.016–0.03		
erm(B) + *mef*(A)	0.03		
L4	0.25–16.0	4.0	8.0
23S rRNA	0.03		
Imipenem			
S	≤0.004–0.5	0.125	0.25
R	≤0.004–2.0	0.06	0.25
erm(B)	≤0.004–2.0	0.125	0.25
mef(A)	≤0.004–0.5	0.016	0.25
erm(A)	≤0.004–0.008		
erm(B) + *mef*(A)	0.008		
L4	0.125–0.25	0.25	0.25
23S rRNA	≤0.004–0.03		
Meropenem			
S	0.008–1.0	0.25	0.5
R	0.008–2.0	0.125	0.5
erm(B)	0.008–2.0	0.25	0.5
mef(A)	0.016–2.0	0.03	0.5
erm(A)	0.008–0.016		
erm(B) + *mef*(A)	0.016		
L4	0.125–1.0	0.5	0.5
23S rRNA	0.016–0.06		

Drug, macrolide susceptibility,[a] and resistance mechanism	MIC (μg/ml)		
	Range	50%	90%
Ceftriaxone			
S	0.016–4.0	0.5	1.0
R	0.008–>8.0	0.25	2.0
erm(B)	0.016–>8.0	0.5	2.0
mef(A)	0.016–4.0	0.06	1.0
erm(A)	0.03		
erm(B) + *mef*(A)	0.03		
L4	0.5–>8.0	2.0	4.0
23S rRNA	0.008–0.125		
Cefuroxime			
S	0.016–16.0	4.0	8.0
R	0.016–64.0	0.5	8.0
erm(B)	0.016–64.0	4.0	8.0
mef(A)	0.03–8.0	0.125	8.0
erm(A)	0.03		
erm(B) + *mef*(A)	0.03		
L4	4.0–64.0	8.0	32.0
23S rRNA	0.03–0.5		
Cefpodoxime			
S	0.03–8.0	1.0	4.0
R	0.03–64.0	0.5	4.0
erm(B)	0.03–64.0	2.0	4.0
mef(A)	0.03–8.0	0.06	4.0
erm(A)	0.03		
erm(B) + *mef*(A)	0.03		
L4	2.0–32.0	4.0	32.0
23S rRNA	0.03–0.125		
Cefdinir			
S	0.016–16.0	4.0	8.0
R	0.03–>64.0	0.5	8.0
erm(B)	0.03–>64.0	4.0	8.0
mef(A)	0.03–16.0	0.125	8.0
erm(A)	0.06		
erm(B) + *mef*(A)	0.06		
L4	4.0–32.0	8.0	16.0
23S rRNA	0.06–0.125		
Azithromycin			
S	≤0.016–0.125	0.125	0.125
R	1.0–>64.0	>64.0	>64.0
erm(B)	2.0–>64.0	>64.0	>64.0
mef(A)	1.0–>64.0	4.0	16.0
erm(A)	4.0–8.0		
erm(B) + *mef*(A)	>64.0		
L4	>64.0	>64.0	>64.0
23S rRNA	>64.0		
Clarithromycin			
S	≤0.016–0.06	0.03	0.03
R	0.5–>64.0	64.0	>64.0
erm(B)	0.5–>64.0	>64.0	>64.0
mef(A)	0.5–32.0	2.0	8.0
erm(A)	0.5–1.0		
erm(B) + *mef*(A)	>64.0		
L4	8.0–64.0	32.0	64.0
23S rRNA	8.0–16.0		

[a] S, susceptible (n = 146); R, resistant (n = 154). The 154 resistant isolates had the following resistance mechanisms: *erm*(B), n = 87; *mef*(A), n = 40; *erm*(A), n = 4; *erm*(B) and *mef*(A), n = 1; L4 protein mutation (L4), n = 18; and 23S rRNA mutation (23S rRNA), n = 4.

TABLE 3. MICs for 12 strains tested by time-kill method

Drug	MIC (μg/ml) for strain:											
	1[a]	2[a]	3[a]	4[a]	5[b]	6[b]	7[b]	8[b]	9[c]	10[c]	11[d]	12[d]
LBM415	0.12	2.0	2.0	2.0	0.12	0.25	0.5	0.25	0.5	0.5	0.5	1.0
Amoxicillin	0.016	2.0	2.0	2.0	0.25	0.03	0.06	0.06	2.0	2.0	2.0	0.03
Amoxicillin-clavulanate	0.016	2.0	2.0	2.0	0.12	0.03	0.03	0.12	2.0	2.0	2.0	0.016
Imipenem	0.004	0.25	0.25	0.25	0.03	0.008	0.008	0.03	0.25	0.12	0.25	0.008
Meropenem	0.008	0.5	0.5	1.0	0.06	0.016	0.016	0.06	0.5	0.25	0.5	0.016
Ceftriaxone	0.016	2.0	2.0	2.0	0.12	0.016	0.06	0.06	2.0	2.0	4.0	0.03
Cefuroxime	0.016	2.0	2.0	4.0	0.25	0.03	0.12	0.25	8.0	16.0	16.0	0.03
Cefdinir	0.06	4.0	4.0	4.0	0.12	0.12	0.03	0.06	8.0	8.0	16.0	0.12
Ciprofloxacin	1.0	1.0	1.0	1.0	1.0	4.0	4.0	2.0	2.0	1.0	8.0	>32.0
Levofloxacin	1.0	1.0	1.0	1.0	1.0	2.0	1.0	1.0	2.0	1.0	8.0	16.0
Gatifloxacin	1.0	0.5	0.5	0.5	0.5	0.5	0.5	0.25	0.5	0.5	4.0	8.0
Moxifloxacin	0.12	0.25	0.25	0.25	0.25	0.25	0.25	0.12	0.25	0.25	2.0	4.0
Azithromycin	>64	>64	>64	>64	8.0	8.0	16.0	2.0	>64	>64	0.06	0.125
Clarithromycin	64	>64	>64	>64	2.0	4.0	8.0	2.0	16	32	0.016	0.03
Linezolid	0.5	2.0	1.0	1.0	0.5	1.0	1.0	0.5	2.0	2.0	1.0	1.0
Quinupristin-dalfopristin	0.5	1.0	0.5	0.5	0.25	0.25	0.5	0.25	0.5	0.5	0.25	0.25
Daptomycin	0.12	0.25	0.25	0.5	0.12	0.25	0.25	0.25	0.25	0.25	0.12	0.25
Vancomycin	0.25	0.5	0.5	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.5
Teicoplanin	0.06	0.12	0.06	0.12	0.06	0.12	0.12	0.06	0.06	0.12	0.12	0.06

[a] Macrolide-resistant strains carrying the *erm*(B) mutation.
[b] Macrolide-resistant strains carrying the *mef*(A) mutation.
[c] Macrolide-resistant strains carrying an L4 protein mutation.
[d] Quinolone-resistant strains (ciprofloxacin MIC, ≥8.0 μg/ml).

TABLE 4. Pneumococcal killing kinetics results

Drug and multiple of MIC	No. of isolates for which the level of killing[a] was as indicated at the following times:											
	3 h			6 h			12 h			24 h		
	−1	−2	−3	−1	−2	−3	−1	−2	−3	−1	−2	−3
LBM415												
4	0	0	0	4	1	0	9	2	2	12	9	8
2	0	0	0	3	1	0	9	2	2	10	8	6
1	0	0	0	2	0	0	8	1	1	7	4	2
Amoxicillin												
4	12	7	0	12	11	6	12	12	11	12	12	12
2	9	4	0	12	10	6	12	11	10	12	12	12
1	7	3	0	10	9	3	12	10	8	12	11	9
Amoxicillin-clavulanate												
4	11	6	1	12	11	7	12	11	10	12	12	12
2	10	6	1	12	11	7	12	11	10	12	12	12
1	9	3	1	12	10	3	12	11	9	11	11	10
Imipenem												
4	12	7	0	12	10	5	12	12	11	12	12	12
2	12	5	0	12	10	5	12	12	11	12	12	12
1	11	4	0	11	6	4	12	11	8	12	11	10
Meropenem												
4	11	4	2	12	9	3	12	12	10	12	12	12
2	9	3	1	12	7	3	12	11	9	12	12	12
1	8	2	1	11	7	3	11	7	4	8	7	5
Ceftriaxone												
4	7	2	0	12	6	2	12	12	10	12	12	12
2	6	2	0	12	7	3	12	12	10	12	11	10
1	4	1	0	8	5	3	9	9	6	11	8	4
Cefuroxime												
4	11	3	2	12	10	3	12	11	10	12	12	12
2	11	3	0	12	9	3	12	11	10	12	12	11
1	9	1	0	12	9	2	12	11	9	11	10	9

Continued on following page

TABLE 4—*Continued*

Drug and multiple of MIC	No. of isolates for which the level of killing[a] was as indicated at the following times:											
	3 h			6 h			12 h			24 h		
	−1	−2	−3	−1	−2	−3	−1	−2	−3	−1	−2	−3
Cepodoxime												
4	11	3	0	12	12	4	12	12	10	12	12	12
2	11	3	0	12	12	3	12	12	10	12	12	12
1	9	2	0	12	10	3	12	10	9	12	11	11
Cefdinir												
4	10	5	1	12	9	5	12	12	11	12	12	12
2	9	3	0	12	9	5	12	11	10	12	12	12
1	4	3	0	10	6	2	12	7	4	9	7	5
Ciprofloxacin[b]												
4	9	6	0	10	10	4	10	10	10	10	10	10
2	9	3	0	10	10	3	10	10	7	10	9	9
1	6	1	0	9	6	1	10	9	4	8	7	5
Levofloxacin[b]												
4	7	2	0	10	10	3	10	10	10	10	10	10
2	5	0	0	10	6	1	10	10	6	10	10	10
1	5	0	0	8	4	1	10	8	3	9	9	5
Gatifloxacin[b]												
4	10	3	0	10	8	1	10	10	8	10	10	9
2	6	1	0	10	7	1	10	10	7	10	10	9
1	4	0	0	7	2	1	10	6	3	9	8	4
Moxifloxacin[b]												
4	10	3	0	10	10	3	10	10	9	10	10	10
2	8	1	0	10	6	2	10	10	9	10	10	10
1	5	0	0	8	4	1	9	8	5	10	8	7
Azithromycin[c]												
4	2	0	0	2	1	1	2	2	2	2	2	2
2	1	0	0	1	1	1	2	2	2	2	2	2
1	1	0	0	1	1	1	2	1	1	2	2	2
Clarithromycin[c]												
4	0	0	0	2	2	0	2	2	2	2	2	2
2	0	0	0	2	2	0	2	2	2	2	2	2
1	0	0	0	2	1	0	2	2	2	2	2	2
Linezolid												
4	1	0	0	9	1	1	12	7	3	12	12	9
2	0	0	0	4	1	1	11	4	1	12	11	7
1	0	0	0	2	0	0	6	1	0	8	4	2
Quinupristin-dalfopristin												
4	11	10	6	12	11	9	12	11	11	12	12	12
2	11	9	5	12	11	9	12	11	11	12	12	12
1	10	7	4	12	11	6	11	10	7	7	5	3
Daptomycin												
4	11	8	2	12	11	9	12	11	11	12	12	12
2	10	4	2	12	11	8	12	11	11	12	11	11
1	7	2	2	12	11	4	11	10	7	8	5	3
Vancomycin												
4	4	2	0	12	6	3	12	11	10	12	12	12
2	4	1	0	12	6	3	12	11	9	12	12	12
1	4	0	0	12	5	2	12	11	9	11	10	9
Teicoplanin												
4	0	0	0	6	1	0	11	7	4	12	12	11
2	0	0	0	6	1	0	10	7	4	12	12	10
1	0	0	0	5	1	0	9	6	3	9	8	7

[a] −1, −1 $\log_{10}$ CFU/ml (90% killing); −2, −2 $\log_{10}$ CFU/ml (99% killing); −3, −3 $\log_{10}$ CFU/ml (99.9% killing).
[b] Ten strains for which the ciprofloxacin MIC was <8.0 μg/ml were tested.
[c] Two macrolide-sensitive strains (erythromycin MIC, 0.03 μg/ml) were tested.

deformylase inhibitor, NVP-PDF386 (VCR4887), showed MICs for β-lactam- and macrolide-susceptible and -resistant pneumococci which ranged from ≤0.016 to 1.0 μg/ml, with an MIC_{50} of 0.25 μg/ml and an MIC_{90} of 0.5 μg/ml (14). As was the case with our study, no differences in NVP-PDF386 MICs were found between drug-resistant and drug-susceptible pneumococcal strains (14). The results of the present study confirm the low MICs of LBM415 for pneumococci. Susceptibility breakpoints have not yet been established for LBM415, so the significance of the MIC range cannot be interpreted at this time. However, all strains were susceptible (MICs, ≤4.0 μg/ml).

LBM415 was slowly bactericidal, with 99.9% killing of 8 of 12 strains at four times the MIC after 24 h, with slower rates of killing at lower concentrations and earlier time periods. By comparison, daptomycin and quinupristin-dalfopristin have the most rapid killing, followed by the quinolones, the β-lactams, and the macrolides. The results for the last three groups of compounds have been published previously (4, 5, 8–11, 16, 18–25).

Craig and Andes (W. A. Craig and D. R. Andes, Abstr. 14th Eur. Congr. Clin. Microbiol. Infect. Dis., abstr. P921 and P922, 2004) have shown that the 24-h area under the concentration-time curve (AUC)/MIC ratio is the parameter that best correlates with the in vivo activity of LBM415 in mice. The drug also has a prolonged in vivo postantibiotic effect, suggesting twice-daily dosing. For pneumococci, the mean free AUC/MIC ratio was 34.9 ± 7.1, with bacteriostatic doses ranging from 47.6 to 81.3 mg/kg of body weight/6 h.

The results of this study indicate a potential role for LBM415 in the treatment of pneumococcal infections. However, interpretation of these in vitro results must be complemented by toxicity and human pharmacokinetic and pharmacodynamic studies (not available at present) before the drug can be recommended for clinical testing.

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