Antimicrobial Spectrum and Activity of LBM415, a Novel Peptide Deformylase Inhibitor, Tested Against 1,837 Recent Gram-Positive Clinical Isolates

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ABSTRACT

Background: The continued development and expansion of resistances (R) among Gram-positive pathogens (GPP) has threatened the therapy of numerous antimicrobial classes including the recently introduced quinupristin/dalfopristin, telithromycin and the oxazolidinones. Clearly the need for antimicrobial discovery persists, and this should be a continued priority for the pharmaceutical industry. This report addresses the spectrum of activity for LBM415 tested against a collection of recent (2002) clinical isolates cultured from patients infected with pathogens within the spectrum for peptide deformylase inhibitors. ***Methods***: LBM415 was acquired from Novartis. The compound was dispensed into reference broth microdilution trays in appropriate media over the range of 0.06 to 8 mg/L. Mueller-Hinton broth was supplemented with 2 - 5% lysed horse blood when testing fastidious streptococci, and the Corynebacteria. NCCLS QC strains were used concurrently and all LBM415 MIC results were within proposed ranges. ***Results***: 1,837 Gram-positive strains were tested with a species rank order of *S. aureus* (875 strains) > CoNS (381) > streptococci (285) > enterococci (273) > *Listeria* spp. (11). The LBM415 MIC results against *S. aureus* and the CoNS strains ranged from ≤0.06 to 4 mg/L, but the vast majority of staphylococci (87.0%) had MICs of 0.25 - 2 mg/L. Staphylococcal MIC_{90} results for LBM415 were 1 or 2 mg/L, regardless of oxacillin R pattern. Also tested were *Corynebacterium* spp. (8 strains; LBM415 MIC_{50}, 0.25 mg/L), *Bacillus* spp. (3; MIC_{50}, 0.12 mg/L) and one *Micrococcus* spp. (MIC, 0.25 mg/L). LBM415 MICs for enterococci ranged to > 8 mg/L, but 99.3% of strains were inhibited at ≤ 8 mg/L, the proposed susceptible breakpoint. R to other classes of agents did not influence the LBM415 MIC values among enterococci. All streptococci were inhibited at ≤ 4 mg/L, and the β-haemolytic and *S. bovis* strains were susceptible to LBM415 at ≤ 1 mg/L. Previous reports have shown that > 90% of *H. influenzae* (MIC_{90}, 8 mg/L) and all *M. catarrhalis* (MIC_{90}, 0.5 mg/L) are inhibited by LBM415. ***Conclusions***: To address the established decline in potency or coverage of GPP by existing antimicrobials, LBM415 appears to be a promising new agent applicable by oral and parenteral routes. The combined spectrum of activity against MRSA, VRE, DRSP and key Gram-negative community-acquired respiratory tract pathogens warrants further investigations of LBM415 in human trials.

INTRODUCTION

- The development and expansion of resistances among gram-positive pathogens has threatened the potential therapy with numerous antimicrobial classes including the recently introduced streptogramin combination (quinupristin/dalfopristin), a ketolide (telithromycin) and the oxazolidinone (linezolid).
- Examples of the more serious resistance problems have been the escalated rates of occurrence for methicillin-resistant staphylococci (MRSA), vancomycin-resistant enterococci (VRE), glycopeptide- or vancomycin-intermediate or -resistant *Staphylococcus aureus* (VRSA or VISA) and multi-drug resistant *Streptococcus pneumoniae* (DRSP).
- Clearly the need for antimicrobial discovery and research persists, and this should be a continued priority for the pharmaceutical industry worldwide.
- One novel class of antimicrobial agents exploits the peptide deformylase target of protein synthesis described over 3 decades ago.
- Several candidate compounds in this new class have been described, but few have progressed to expanded studies in human subjects. Among the most promising have been the synthetic hydroxamic acid derivatives including the compound LBM415.
- This agent has been characterized as having activity against major respiratory tract pathogens (*S. pneumoniae, Haemophilus influenzae, Moraxella catarrhalis,* atypical species), and also retains a useable potency versus MRSA, VRE and other resistant gram-positive organisms.
- Early *in vitro* studies of these compounds have generally focused on antimicrobial-resistant organism populations, not routine clinical isolates from a wide geographic sample. This report addresses the spectrum of activity for LBM415 tested against a collection of recent clinical isolates (2002 from North America and Europe) cultured from patients infected with pathogens within the proposed spectrum for peptide deformylase inhibitors.

METHODS

- LBM415 was acquired from Novartis Pharmaceuticals (Basel, Switzerland).
- The compound was dispensed into broth microdilution trays by TREK Diagnostics (Cleveland, Ohio, USA) in appropriate media over the concentration range of 0.06 to 8 mg/L (8 $\log_2$ dilutions) and kept at -70ºC until used.
- Mueller-Hinton broth was supplemented with 2–5% lysed horse blood when testing fastidious streptococci, and the Corynebacteria.
- All methods utilized conformed to the recommendations of the National Committee for Clinical Laboratory Standards (NCCLS) M7-A6.
- Resistance subcategories within tested species were selected using the breakpoint criteria of the NCCLS [2003b] for oxacillin (MRSA), vancomycin (VRE) and penicillin (DRSP).
- NCCLS quality control strains *S. aureus* ATCC 29213, *Enterococcus faecalis* ATCC 29212, and *S. pneumoniae* ATCC 49619 were used concurrently and all LBM415 MIC results were within proposed ranges published by Anderegg *et al.*

RESULTS

- During the study interval, a total of 1,837 gram-positive strains (Table 1) were tested with a species rank order of *S. aureus* (875 strains) > coagulase-negative staphylococci (CoNS; 381 strains) > streptococci (285 strains) > enterococci (273 strains) > *Listeria* spp. (11 strains).
- Also tested (not found in Table 1) were *Corynebacterium* spp. (8 strains; LBM415 MIC_{50}, 0.25 mg/L), *Bacillus* spp. (3 strains; MIC_{50}, 0.12 mg/L) and 1 isolate of *Micrococcus* spp. (MIC, 0.25 mg/L). The highest MIC for LBM415 recorded for these 3 genus groups was only 0.5 mg/L.
- The LBM415 MIC results against *S. aureus* and the CoNS strains ranged from ≤0.06 to 4 mg/L, but the vast majority of staphylococci (87.0%) had MIC values between 0.25 and 2 mg/L. Staphylococcal MIC_{90} results for LBM415 were either 1 or 2 mg/L, regardless of the resistance pattern to oxacillin (data not shown).
- Among the enterococci, LBM415 potency was generally 2-fold lower when compared to its anti-staphylococcal potency (Table 1). LBM415 MIC results for enterococci ranged to > 8 mg/L, but 99.3% of strains were inhibited at ≤ 8 mg/L, the tentative susceptible breakpoint.
- Resistances to other classes of agents did not influence the LBM415 MIC values among enterococci (data not shown).
- Based on the MIC_{90} results, the pneumococci were slightly less susceptible to LBM415 compared to the other streptococci (MIC_{90}, 1 versus 2 mg/L). All streptococci were inhibited at ≤ 4 mg/L, and the β-haemolytic and *S. bovis* strains were susceptible to LBM415 at ≤ 1 mg/L. Previous reports have shown that > 90% of *H. influenzae* (MIC_{90}, 8 mg/L) and all *M. catarrhalis* (MIC_{90}, 0.5 mg/L) are inhibited by LBM415.

CONCLUSIONS

- The combined spectrum of activity against MRSA, VRE, DRSP and key gram-negative community-acquired respiratory tract pathogens (reported elsewhere, LBM415 MIC_{90}= 8 mg/L) warrants further investigation of LBM415 in human trials.
- To address the established decline in potency or coverage of gram-positive pathogens by existing antimicrobial agents, LBM415 appears to be a promising compound to be applied by oral and parenteral routes.

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TABLE 1. Activity and spectrum of LBM415, a peptide deformylase inhibitor, tested against 1,825 gram-positive organisms from year 2002[a]

	MIC (mg/L)			Cumulative % inhibited at MIC (mg/L)							
Organism (no. tested)	50%	90%	Range	≤0.06	0.12	0.25	0.5	1	2	4	8
S. aureus (875)	0.5	1	≤0.06-4	2.1	11.3	23.3	54.4	83.1	99.9	100.0	–
Coagulase-negative staphylococci (381)	1	2	≤0.06-4	8.4	15.0	24.1	43.3	81.1	98.4	100.0	–
Enterococci (273)	2	4	≤0.06->8	0.4	1.8	7.7	17.6	38.8	68.5	97.8	99.3
Streptococci											
S. pneumoniae (95)	0.5	2	≤0.06-4	7.4	12.6	32.6	56.8	77.9	93.7	100.0	–
β-haemolytic (95)	0.25	1	≤0.06-1	4.2	13.7	50.5	72.6	100.0	–	–	–
Viridans group (82)	0.25	1	≤0.06-4	24.4	43.9	66.3	86.6	98.8	98.8	100.0	–
S. bovis (13)	0.5	1	≤0.06-1	30.8	38.5	46.2	84.6	100.0	–	–	–
Listeria spp. (11)	1	2	1-2	0.0	0.0	0.0	0.0	54.5	100.0	–	–

a. All tests were performed with the reference broth microdilution method [NCCLS, 2003a].