Antimicrobial Activity of LBM 415 (NVP PDF-713) Tested Against *Neisseria meningitidis* and *N. gonorrhoeae*

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ABSTRACT

Background: LBM 415 (415), a peptide deformylase inhibitor will be advanced into clinical trials (oral and parenteral routes) for treatment of community-acquired respiratory infections, among other indications, and has demonstrated activity against *N. meningitidis* (NM). In this study we evaluate the potency of 415 against a challenge set of strains consisting of pathogenic neisserias.

Methods: 157 strains of *N. gonorrhoeae* (NG), including strains with elevated MICs to fluoroquinolones, ß-lactams and tetracyclines, were tested by the NCCLS agar dilution method using GC agar base with defined supplement against 415, penicillin (PEN), ceftriaxone (CTR), tetracycline (TET) and ciprofloxacin (CIP). 100 strains of NM (96 isolated from blood), including strains with elevated PEN MIC values, were tested using Mueller-Hinton agar with 5% sheep blood. Five NM strains were tested by agar dilution and broth microdilution MIC methods to validate the agar dilution method. Absolute agreement occurred with 4 of 5 identical MIC results, and all results were within ± one $\log_2$ dilution step.

Results: The ranking of most to least active compound (and MIC ranges) when testing NM was: CTR (≤ 0.001-0.008 µg/ml); CIP (≤ 0.004-0.008 µg/ml); PEN (0.016-0.25 µg/ml); TET (0.12-1 µg/ml); and 415 (0.5-4 µg/ml). 415 was the least active, but all MICs were ≤ 4 µg/ml with a $MIC_{50/90}$ of 1 and 2 µg/ml. Testing of 157 NG strains showed a generally higher 415 MIC when compared to the NM results, the ranking (and MIC range) being: CTR (≤ 0.001-0.12 µg/ml); CIP (≤ 0.004-2 µg/ml); TET (0.008- ≤ 2 µg/ml); PEN (0.016- ≤ 2 µg/ml); and 415 (0.06-32 µg/ml). 415 was the least active against NG, with a $MIC_{50/90}$ of 4 and 8 µg/ml. Only one NG had a 415 MIC at >16 µg/ml (potential resistance).

Conclusions: 415 had an acceptable potency against NM but was two- to four-fold less active against NG. While the in vitro activity of 415 against targeted bacterial species, including NM, makes this a promising compound for treatment of respiratory tract disease, there appears to be limited utility against the related species NG.

INTRODUCTION

LBM415 (NVP PDF-713) is the first inhibitor of the bacterial enzyme peptide deformylase (PDF) to be advanced into human clinical trials for the oral or parenteral treatment of community-acquired respiratory tract, and skin and skin structure infections. PDF is required in bacteria for protein maturation and is not found in eukaryotic cells, making it a unique antibacterial target. LBM415 has documented activity against major pathogens including *Streptococcus pneumoniae* (penicillin-susceptible and -resistant), *Haemophilus influenzae, Moraxella catarrhalis, Chlamydia pneumoniae, Staphylococcus aureus* (oxacillin-susceptible and –resistant), ß-haemolytic streptococci, enterococci (vancomycin-susceptible and -resistant); co-resistance with other classes of antimicrobials has not been detected.

While preliminary studies have included data on a variety of respiratory tract and skin and soft tissue pathogens, nothing has been published on its activity against the pathogenic neisserieae, i.e. *N. meningitidis* and *N. gonorrhoeae*. The recent emergence of resistance to fluoroquinolones among other agents used in the treatment of gonococcal disease stresses the need to evaluate new compounds having novel targets of action.

This report summarizes the antimicrobial activity of LBM415 against clinical isolates of *N. meningitidis* and *N. gonorrhoeae* originating from a worldwide collection that includes representative resistant phenotypes.

MATERIALS AND METHODS

- The collection consisted of 100 *N. meningitidis* (96 bloodstream isolates) and 157 *N. gonorrhoeae,* and were obtained from global surveillance networks. The *N. meningitidis* isolates included strains with elevated penicillin MIC values whereas the *N. gonorrhoeae* isolates included strains resistant to fluoroquinolones, ß-lactams, and tetracyclines.
- The agar dilution method as defined by the National Committee for Clinical Laboratory Standards (NCCLS) in the M7-A6 document (2003) using GC agar base with defined supplement was used for testing of *N. gonorrhoeae.* Isolates of *N. meningitidis* were tested using the agar dilution method with Mueller-Hinton agar supplemented with 5% defibrinated sheep blood [NCCLS, 2005]. A subset of 5 *N. meningitidis* strains was tested by both agar dilution and NCCLS broth microdilution methods to validate the agar dilution method. Interpretive criteria utilized were those of the NCCLS [2004 and 2005].
- LBM415 (NVP PDF-713) reagent-grade powder was provided by Novartis (Basel, Switzerland). Comparator agents (penicillin, ceftriaxone, ciprofloxacin and tetracycline) were purchased from Sigma Chemical Company (St. Louis, MO, USA) or provided by the respective manufacturer in the USA.

RESULTS

- The activity profile of LBM415 and comparator agents tested against 100 strains of *N. meningitidis* and 157 strains of *N. gonorrhoeae* is presented in Table 1.
- Results for LBM415 tested by both agar dilution and broth microdilution methods against 5 stains of *N. meningitidis* are presented in Table 2; agreement was identical for four of the five MIC results and all results were within ± one $\log_2$ dilution.
- Nearly all *N. meningitidis* strains (96 of 100) were isolated from bloodstream infections with an overall penicillin susceptibility rate of 68% (MIC, ≤ 0.06 µg/ml).
- Ceftriaxone was the most active compound against *N. meningitidis* (MIC_{90}, 0.002 µg/ml), followed by ciprofloxacin (0.008 µg/ml), penicillin = tetracycline (0.25 µg/ml), and LBM415 (2 µg/ml).
- While LBM415 was the least active antimicrobial agent tested against *N. meningitidis,* the MIC_{50} was 1 µg/ml and all isolates were inhibited by 4 µg/ml, the latter being a level where most strains would be expected to respond, given recorded pharmacokinetic/pharmacodynamic studies.
- Testing of *N. gonorrhoeae* isolates, including those with resistances to other antimicrobial classes (tetracycline, 31.8% susceptible; penicillin, 5.7% susceptible; ciprofloxacin, 15.9% non-susceptible), showed generally higher LBM415 MIC values than recorded for *N. meningitidis*, with the $MIC_{50/90}$ being 4/8 µg/ml.
- Only one gonococcus had a LBM MIC at >16 µg/ml, indicating potential resistance.

TABLE 1. MIC distributions for 100 *N. meningitidis* and 158 *N. gonorrhoeae* strains tested against LBM-415 and four comparison agents.

Organisms/antimicrobial agent (no. tested)	No. of occurrences at MIC (µg/ml)[a]																
	≤0.001	0.002	0.004	0.008	0.016	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	>
N. meningitidis (100)[b]																	
NVP PDF-713	-	-	-	-	-	-	-	-	-	3	75	18	4	-	-	-	0
Tetracycline	-	-	-	-	-	-	-	4	91	2	3	-	-	-	-	-	0
Penicillin	-	-	-	-	20	33	15	17[c]	15[c]	-	-	-	-	-	-	-	0
Ciprofloxacin	-	-	33	67	-	-	-	-	-	-	-	-	-	-	-	-	0
Ceftriaxone	78	21	-	1	-	-	-	-	-	-	-	-	-	-	-	-	0
N. gonorrhoeae (157)																	
NVP PDF-713	-	-	-	-	-	-	1	4	2	3	26	37	49	27	7	1	0
Tetracycline	-	-	-	1	1	0	7	13	28	34	26	24	NT	NT	NT	NT	23
Penicillin	-	-	-	-	3	4	2[c]	17	15	11	29	38	NT	NT	NT	NT	38
Ciprofloxacin	NT	NT	85	9	20	10	8	5	17	0	1	2	-	-	-	-	0
Ceftriaxone	12	11	44	38	25	10	10	7	-	-	-	-	-	-	-	-	0

a. MIC values were determined by the agar dilution method (Mueller-Hinton agar + 5% sheep blood for meningococci and GC agar base with defined supplement for gonococci) [NCCLS, 2003].
b. 32 strains with elevated penicillin MIC results (MIC, > 0.06 µg/ml) were tested.
c. Only 5.7% of isolates were penicillin-susceptible.

TABLE 2. MIC results for five *N. meningitidis* strains tested by agar dilution and broth microdilution methods against LBM415.

Organism no.	MIC (µg/ml) by method	
	Agar	Broth
25-342	2	2
42-43	1	0.5
42-244	2	2
42-2283	4	4
301-2442	1	1

CONCLUSIONS

- LBM415 demonstrated acceptable activity against *N. meningitidis* isolates with a $MIC_{50/90}$ of 1/2 µg/ml and all isolates being inhibited by ≤ 4 µg/ml.
- Activity ($MIC_{50/90}$, 4/8 µg/ml) of LBM415 against *N. gonorrhoeae* was 4-fold less active when compared to *N. meningitidis*. Only one *N. gonorrhoeae* isolate had a LBM415 MIC indicating potential resistance.
- LBM415, displaying a novel target mechanism of action, has emerged as a promising therapeutic option for the treatment of infections caused by *N. meningitidis* but provides a more limited coverage of *N. gonorrhoeae*.

REFERENCES

Antignac A, Ducos-Galand M, Guiyoule A, Pires R, Alonso JM, Taha MK. (2003). *Neisseria meningitidis* strains isolated from invasive infections in France (1999-2002): Phenotypes and antibiotic susceptibility patterns. *Clinical Infectious Disease* 37:912-920.

Bozdogan B, Esel D, Whitener C, Browne FA, Appelbaum PC. (2003). Antibacterial susceptibility of a vancomycin-resistant *Staphylococcus aureus* strain isolated at the Hershey Medical Center. *Journal of Antimicrobial Chemotherapy* 52:864-868.

Chen D, Hackbarth C, Ni ZJ, Wu C, Wang W, Jain R, He Y, Bracken K, Weidmann B, Patel DV, Trias J, White RJ, Yuan Z. (2004). Peptide deformylase inhibitors as antibacterial agents: Identification of VRC3375, a proline-3-alkylsuccinyl hydroxamate derivative, by using an integrated combinatorial and medicinal chemistry approach. *Antimicrobial Agents and Chemotherapy* 48:250-261.

Jones RN, Fritsche TR, Sader HS. (2004). Antimicrobial spectrum and activity of NVP PDF-713, a novel peptide deformylase inhibitor, tested against 1,837 recent Gram-positive clinical isolates. *Diagnostic Microbiology and Infectious Disease* 49:63-65.

Kam KM, Kam SSY, Chueng DTL, Tung VWA, Au WF, Cheung MM. (2003). Molecular characterization of quinolone-resistant *Neisseria gonorrhoeae* in Hong Kong. *Antimicrobial Agents and Chemotherapy* 47:436-439.

National Committee for Clinical Laboratory Standards. (2003). *Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically. Document M7-A6*. Wayne, PA:NCCLS.

National Committee for Clinical Laboratory Standards. (2005). *Performance standards for antimicrobial susceptibility testing M100-S15*. Wayne, PA:NCCLS (publication, January 2005).

Wise R, Andrews JM, Ashby J. (2002). In vitro activities of peptide deformylase inhibitors against Gram-positive pathogens. *Antimicrobial Agents and Chemotherapy* 46:1117-1118.