In Vitro Activity of the Novel Pleuromutilin BC-3781 Tested Against Bacterial Pathogens Causing Sexually Transmitted Diseases (STD)

Paukner S.1, Gross A.2, Fritsche T.R.2, Ivezic-Schoenfeld Z.1, Jones R.N.2

1 Nabriwa Therapeutics AG, Vienna, Austria; 2 JMI Laboratories, North Liberty, IA, USA

ABSTRACT

Background: STDs are a significant health challenge in Europe and the USA. Chlamydia trachomatis infection and gonorrhea caused by Neisseria gonorrhoeae are the most frequently reported sexually transmitted and reportable diseases in both areas with high infection rates among young persons particularly women. Increased susceptibility of N. gonorrhoeae isolates to amoxicillin, ceftriaxone, and cefixime, recommended therapies for gonorrhea, is extremely concerning. BC-3781 is a novel pleuromutilin for oral and intravenous administration as treatment of bacterial skin and respiratory infections. This study evaluated its in vitro activity against the most prevalent bacterial pathogens causing STDs.

Methods: The antibacterial activity of BC-3781 and comparators was tested against Chlamydia (serovars A, K, L2 and SA2, n=15) McCoy and HeLa 229 cells and Mycoplasma genitalium (n=15), M. hominis (n=1), Ureaplasma urealyticum (n=1) by broth microdilution methods, N. gonorrhoeae (n=4), the anaerobe Peptostreptococcus spp. (n=10) and Prevotella spp. (n=11) were tested by agar dilution methods (CLSI).

Results: BC-3781 demonstrated potent activity against C. trachomatis including serovars causing lymphogranuloma venereum with MICs of 0.02-0.12 µg/mL (range 0.01-0.04 µg/mL). This was comparable to the activity of doxycycline, ceftriaxone and doxycycline and 5-8 fold more active than azithromycin or erythromycin (MICmin/0.1-0.2 µg/mL). BC-3781 was also active against N. gonorrhoeae (MICmin/0.12-0.25 µg/mL) with clindamycin- and tetracycline-resistant strains being inhibited by BC-3781. BC-3781 demonstrated also activity against Mycoplasma spp. including the macrolide-resistant M. hominis (0.04 µg/mL), multi-resistant M. genitalium (0.016-0.063 µg/mL) and against U. urealyticum (1.6 µg/mL). All Peptostreptococcus spp. and 80% of Prevotella spp. isolates were inhibited by BC-3781 concentrations of 2 µg/mL. Porphyromonas was highly susceptible to BC-3781 with MICs of 0.03 µg/mL. Good BC-3781 activity was also demonstrated against H. ducreyi (MIC: 0.015-0.25 µg/mL).

Conclusion: Overall, BC-3781 displayed potent activity against the relevant sexual pathogen causing STD warranting further investigations on the potential of BC-3781 in this indication.

INTRODUCTION

Sexually transmitted diseases (STDs) are a significant health challenge in the USA and in Europe. Infections caused by the bacterium C. trachomatis accounted for 1.4 million cases in 2011 in the USA. The Centers for Disease Control and Prevention (CDC) reports gonorrhea (GC) (Caused by Neisseria gonorrhoeae) as one of the 10 most common reportable infectious diseases. CDC estimates that 800,000 cases occur each year.1 Overall, Chlamydia and GC are the most frequently reported sexually transmitted infections (STIs). C. trachomatis, N. gonorrhoeae, and other sexually transmitted pathogens, particularly for women, including chronic pelvic pain, threatening ectopic pregnancy, pelvic inflammatory disease and infertility.2 Gonorrhea infection also increases a person's risk of contracting and transmitting HIV.3

Control strategies rely on effective antibiotic therapy. STDs are progressive diseases that can lead to irreversible and serious consequences if left untreated. Newer antibiotics overcoming those infections, preferably available as oral formulations, are therefore urgently needed. BC-3781 is a novel pleuromutilin antibiotic in development for oral and intravenous treatment in the treatment of respiratory and skin infections. In this study, the study evaluated the in vitro activity of BC-3781 against the most prevalent pathogens causing STDs. This included C. trachomatis, gonococci, mycoplasmas, uropathogens and anaerobic cocci and bacilli causing gonorrhea, non-gonococcal urethritis, cervicitis and pelvic inflammatory disease.

METHODS

C. trachomatis smokers L434 (ATCC VR-8206), L434 (ATCC VR-993), AG-I, IT-5W-5, BS-IIT-4, BS-IIT-5, BV-IIT-4, BC-3781, GS90, GV98, GS169, SA169, GA169, and GS169 were cultured in McCoy cells (ATCC CRL-1658) and the serovars CG-1 (ATCC VR-8206), CG-16 (ATCC VR-8217), SMCC (ATCC VR-8226). The MICs were determined as described earlier for MICs on microplates of the respective enterococcal strains infected with C. trachomatis (S10) showing turbidity (50 µL per 96-well plate) of glass covers at drug concentrations ranging from 12.5-0.03 µg/mL. After incubation at 26°C (5°C) for 48-72 h the cells were fixed in methanol and incubations were stained with acid fast stain solution. The MIC was defined as the lowest amount of antibiotic at which no inclusion was observed.

Susceptibility testing of M. genitalium (ATCC 25614), M. hominis (ATCC 29144), u. urealyticum (ATCC 27814) was performed by broth microdilution as described earlier. Initial MICs were read when the change of color in the broth was first observed in the control wells (typically after 5-7 days). Susceptibility testing of the multi-drug resistant M. genitalium isolates was performed using the Vero cell culture and quantitative real-time PCR (Q-PCR) method as described earlier.8 Here, the MIC was expressed as the minimal concentration of the test antibiotic causing a ≥99% inhibition of growth when compared to the mean of the control. MICs of genera tested were performed by agar dilution technique as described in CLSI published guidelines.

RESULTS

C. trachomatis

• BC-3781 exhibited potent activity against the intracellular C. trachomatis including serovars A, B, Bc, Causing ocular trachoma, serovars D, E, F, G, J, K, causing genital and ocular chlamydial infections and the LOV strains L2, L3 and SA1 causing lymphogranuloma venereum with MICs of 0.03-0.04 µg/mL (Table 1). This was comparable to the activities of doxycycline, ceftriaxone and doxycycline and 5-8 fold more active than azithromycin or erythromycin.

N. gonorrhoeae

• Against N. gonorrhoeae BC-3781 demonstrated MICmin/0.125-0.5 µg/mL. It was fully active against Fluoroquinolone-, tetracycline- and aminoglycoside-resistant isolates (Table 1).

P. aeruginosa

• BC-3781 demonstrated potent activity against H. ducreyi causing chancroid, a sexually transmitted infection common in Africa and SE Asia, with a MICmin/0.015-0.25 µg/mL, which was equivalent to the activity of clavulanic acid, tetracycline and erythromycin (Table 1). BC-3781 was also active against the tested M. genitalium (MIC: 0.015-0.25 µg/mL).

CONCLUSIONS

The high potency of BC-3781 against A. gonorrhoeae, C. trachomatis, Mycoplasma species, M. ducreyi and anaerobic organisms suggest that BC-3781 could be a promising frontline antibiotic for the treatment of STD such as gonorrhea, non-gonococcal urethritis, cervicitis, chancroid and pelvic inflammatory disease, especially in populations with high resistance rates to standard of care antibiotics.

CONCLUSIONS

• Sexually transmitted diseases represent a major public health crisis; there is multi-drug resistance present and adequate oral therapies are lacking.

• As BC-3781 is available as an intravenous as well as oral formulation (tablet) and active against multi-drug resistant bacterial isolates, further studies are warranted to explore the BC-3781 activity against larger collections of isolates and to demonstrate its activity in human clinical STD trials.

SELECTED REFERENCES

1. CDC. http://www.cdc.gov/std/stats00/2000Chlamydia.htm
8. Lurain, V. Antibiotics in laboratory medicine. 2nd Ed. Lippe, Williams & Wilkins, Philadelphia, USA (2005)