BACTERICIDAL POTENTIAL OF OSCN-, BOVINE LACTOFERRIN AND THEIR COMBINATION ON CLINICAL ISOLATES OF Burkholderia spp.

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INTRODUCTION

Burkholderia cepacia complex (Bcc) bacteria are important opportunistic pathogens in cystic fibrosis (CF). Bcc pulmonary infections are associated with a rapid decline of lung function. Bcc lung infections are difficult to treat due to Bcc inherent resistance to most of the clinically available antibiotics, including aminoglycosides, quinolones, polymyxins, and β-lactams. Identification of new antimicrobials targeting Burkholderia spp. are needed to address this unmet medical need.

The aim of this in vitro study was to test the antibacterial efficacy of Hypothiocyanite (OSCN) and bovine Lactoferrin (bLF) and OSCN/bLF combination (ALX-009) on Bcc CF-clinical isolates.

OSCN/bLF (ALX-009): Scientific and Medical Rationale

In CF patients

1. Defective / abstent CFTR
   ▶ Impaired SCN transport
2. Defective Lactoperoxidase system
   ▶ Decreased OSCN level in lower airways
3. Decreased Lactoferrin level / activity

ALX-009 administered by inhalation

OSCN/bLF compensates defective host protection against microorganisms and provides to CF patients a therapeutic option to fight lung infections

Potentially breaking the vicious circle leading to lethal conditions

CONCLUSIONS

OSCN/bLF (ALX-009):

■ Is able to inhibit the growth of 155 geographic and genetic-diverse CF Burkholderia spp.
■ Has a strong antibacterial potential with a maximal activity after six hours, however benefit lasts up to 24h
■ Has promising efficacy to fight against Burkholderia spp. lung infection in CF patients, a high unmet medical need

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METHODS

Burkholderia spp. CLINICAL ISOLATES:

155 Burkholderia spp. clinical isolates from different geographical origins (Figure 1) and representing the genomovars prevalence in CF patients (Figure 2) were studied.

MICROBIOLOGY ASSAYS*:

1. MIC:
   - OSCN or bLF alone
   - Broth microdilution method CLSI guideline M07-A9
   - bLF: 0.125 to 64 mg/mL
   - OSCN: 25 to 150 µg/mL

2. FIC Index:
   - OSCN and bLF combined
   - Microdilution method
   - bLF: 0.125 to 32 mg/mL
   - OSCN: 25 to 125 µg/mL

3. Time kill curves
   - Macrodilution method CLSI guideline M26-A
   - Time points: 0, 2, 4, 6, and 24h
   - OSCN+bLF: MIC of OSCN and a 25% MIC of OSCN/bLF alone at MIC of OSCN/bLF
   - bLF: alone at MIC of OSCN/bLF

RESULTS

<table>
<thead>
<tr>
<th>GENOMOVAR</th>
<th>Isolates (n=155)</th>
<th>MIC OSCN (µg/mL) 50%</th>
<th>MIC OSCN (µg/mL) 90%</th>
<th>MIC OSCN (µg/mL) 100%</th>
<th>MIC bLF (mg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I (B. cepacia)</td>
<td>8 (6%)</td>
<td>70</td>
<td>88</td>
<td>89</td>
<td></td>
</tr>
<tr>
<td>II (B. multivorans)</td>
<td>39 (25%)</td>
<td>68</td>
<td>93</td>
<td>101</td>
<td></td>
</tr>
<tr>
<td>III (B. cenocepacia)</td>
<td>66 (43%)</td>
<td>71</td>
<td>106</td>
<td>125</td>
<td></td>
</tr>
<tr>
<td>V (B. vietnamiensis)</td>
<td>6 (4%)</td>
<td>64</td>
<td>83</td>
<td>89</td>
<td></td>
</tr>
<tr>
<td>VI (B. dolosa)</td>
<td>9 (6%)</td>
<td>81</td>
<td>116</td>
<td>117</td>
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<tr>
<td>Other Bcc spp.</td>
<td>27 (17%)</td>
<td>63</td>
<td>101</td>
<td>157</td>
<td></td>
</tr>
</tbody>
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Table 1: Values of MIC50, MIC90 and MIC100 obtained with Bcc clinical isolates in presence of OSCN or bLF.

■ OSCN showed growth inhibitory activity on 100% of tested isolates
■ No inhibitory activity was observed with bLF alone except for 9 isolates over the 155 tested. MIC values for these susceptible isolates were between 0.25 and 32 mg/mL

■ OSCN/bLF (ALX-009) combination is able to inhibit the growth of 100% of the tested isolates
■ bLF decreases up to 40% the concentration of OSCN required to inhibit growth when assayed alone (MIC value)
■ 8% of combinations were synergistic and 58% were additive

■ OSCN/bLF (ALX-009) has a strong bactericidal effect
■ After 6h, OSCN/bLF (ALX-009) induces up to 4-log reduction compared to the starting inoculum
■ After 24h, a strong inhibition was maintained with 6- to 8-log reduction compared to the growth control

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