Poster # 285

ACTIVITY OF FUSIDIC ACID AGAINST METHICILLIN-RESISTANT *STAPHYLOCOCCUS AUREUS* (MRSA) ISOLATED FROM CF PATIENTS

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ABSTRACT

The potential clinical impact of MRSA in the pathogenesis of CF is gaining increased attention. Studies have shown that pulmonary function declines with MRSA infection and the mortality rate is increased among MRSA-positive patients. These observations and the expected continued emergence of resistance emphasize the need for effective strategies to prevent and treat MRSA colonization/infection in CF. Foremost among these include the availability of affordable antibiotics optimally formulated to ensure safety, efficacy and to limit long-term development of antimicrobial resistance. The additional recognition of MRSA strains with decreased susceptibility or complete resistance to vancomycin and the increasing prevalence of multiple drug-resistant staphylococci emphasize the critical need for effective alternative antimicrobials with unique modes of action for treatment of staphylococcal infections. Anti-microbial resistance patterns in MRSA collected from pediatric and adult patients treated at different CF centers in the US show that ~70% harbor hospital-associated MRSA, and ~17% community-associated strains. These CF strains show a higher rate of resistance to trimethoprim-sulfamethoxazole of up to 10%, which is usually lower in both types of MRSA. Although clindamycin is often active in vitro, there is a high rate of clindamycin resistance seen in our results and in published reports.

Taksta is a novel oral formulation of fusidic acid (sodium fusidate) (FA) of the fusidane antibiotic class, currently under clinical development in the US for treatment of acute bacterial skin and skin structure infections (ABSSSI). FA has a unique mechanism of action, specifically, inhibition of bacterial protein synthesis by binding to elongation factor G (EF-G), and therefore there is no cross resistance to other antimicrobial classes. Virtually all *S. aureus* isolated in the US are susceptible to FA (MIC_{90}, 0.12 mg/L). In Europe, FA has been used to successfully eradicate *S. aureus* from the lungs of CF patients. When used as monotherapy, resistance has been noted to be a problem in Europe. A new loading dose regimen is being developed in the US that has been shown to be effective in limiting resistance selection. Taksta in its new US dosing regimen has been shown to be safe and comparable to linezolid in a Phase 2 study in ABSSSI. In order to determine the potential for Taksta in treating *S. aureus* infection in CF patients, 40 strains with different genotypes isolated from CF sputum were tested against FA and comparator antibiotics as shown below:

Drug	Range (mg/L)	MIC_{90} (mg/L)
FA (Taksta)	0.12-0.5	0.25
Vancomycin	0.5-1	1
Daptomycin	0.5-1	1
Tigecycline	0.12-0.25	0.25
Azithromycin	1-≥32	≥32
Linezolid	1-4	2

These results indicate that Taksta shows potential for treating MRSA infection in CF patients and should be studied in a clinical trial.

INTRODUCTION

- The clinical impact of MRSA in the pathogenesis of Cystic Fibrosis (CF) has gained increased attention
  - MRSA positive subjects had greater rates of decline of FEV1 and required more antibiotic treatment
- A collaborative study of CF centers in the US showed the pathologic importance of MRSA in CF (Dasenbrook 2010)
  - 19,833 patients aged 6 - 45 years showed the association between respiratory tract MRSA isolates and survival
  - The mortality rate among MRSA positive subjects was 27.7 deaths/1000 patient years as compared to 18.3 deaths/1000 patient years without MRSA
  - Risk of death 1.27 × higher if patient is colonized with MRSA
- Pediatric patients at different CF centers in the US show that ~70% of subjects harbor Hospital acquired-MRSA and ~17% Community acquired-MRSA
- There is a growing need for an oral antibiotic to treat MRSA in chronic diseases
- Fusidic acid is used successfully in Europe to treat MRSA in CF patients
  - In a study of adult CF population with chronic MRSA infection, 5 of 7 subjects showed no evidence of MRSA during and for 6 months following treatment with fusidic acid and rifampin given for 6 months (Garske 2004)
  - In 16 CF children hospitalized with *S. aureus* (Non-MRSA) infections, oral fusidic acid (700-110 mg/M2/D X 14 D) achieved high serum concentrations (10-50 µg/ml) and satisfactory morning sputum concentrations (~0.6 – 4.0 µg/ml) 7 to 14 days after initiating treatment. Eradication of *S. aureus* in sputum samples and clinical improvement was achieved in 14/16 patients (Kraemer 1982)
- Proven efficacy and safety for treating skin infections caused by *Staph. aureus,* including MRSA and beta-hemolytic streptococci
  - Has been used orally in bone and joint infections over extended periods with great success
  - Substantial track record of safety and tolerability through 30+ years of use in over 20 countries in Europe and Asia Pacific
  - Extensive oral use in pediatric populations with excellent safety and tolerability
  - Oral formulation - 98% oral bioavailability
- Positive Phase 2 data supports efficacy and safety
  - Our recent Phase 2 trial in skin infections showed Taksta (Fusidic acid) to be comparable to linezolid (Still 2011)
  - Proprietary loading dose regimen (Okusanya 2011) was well tolerated and overcomes resistance and the need for dual therapy

MATERIALS AND METHODS

Forty MRSA isolated within the past 12 months from patients at Hershey Medical Center's CF clinic, were tested by MICs determination. Only one strain per patient was tested as determined by multiple-locus variable number tandem repeats typing (MLVF, formerly MLVA). Fusidic acid powder was obtained from Cempra Pharmaceuticals, Inc. (Chapel Hill, NC) and other antimicrobial agents were obtained from their respective manufacturers. MICs of each strain to fusidic acid and other comparators were tested by CLSI microdilution methodology. Trays were obtained from Trek, Inc. (Cleveland, OH) or prepared in-house.

RESULTS

Drug	MIC Range (mg/L)	MIC_{50} (mg/L)	MIC_{90} (mg/L)
Fusidic Acid (Taksta)	0.12-0.5	0.12	0.25
Vancomycin	0.5-1	0.5	1
Teicoplanin	0.25-1	0.5	1
Daptomycin	0.5-1	0.5	1
Tigecycline	0.12-0.25	0.12	0.25
Azithromycin	1-≥32	≥32	≥32
Clarithromycin	0.25-≥32	≥32	≥32
Linezolid	1-4	2	2
Quinupristin/dalfopristin	0.25-1	0.5	1

CONCLUSIONS

- Fusidic acid is very effective in vitro against 40 independent clinical isolates of MRSA from CF patients.
- Fusidic acid is used in Europe for decolonization of MRSA from CF patient's lungs.
- Taksta is a novel loading dose formulation of fusidic acid, which significantly decreases the selection of resistant strains and is being developed for monotherapy for treating skin infections.
- Taksta (Fusidic acid) should be studied in clinical trials in the U.S. in CF patients.

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