

Activity of Fusidic Acid Against Methicillin-resistant *Staphylococcus Aureus* (MRSA) Isolated from CF Patients

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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 (MIC₉₀, 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.