Inflammatory Markers in a Phase 1 Placebo Controlled Dose Escalating Study of Intravenous Doses of CF-301 in Human Subjects

A Jandourek[1], J Boyle[2], G Murphy[3], C Cassino[1],

[1]ContraFect Corporation, Yonkers, NY, [2]BCH Research Solutions, West Chester PA, [3] Riverside Consulting, Wilmington DE

Introduction

Lysins are cell wall hydrolases which are produced during the infection cycle of double stranded deoxyribonucleic acid (DNA) bacteriophages to enable the release of progeny virions from the host bacteria. When expressed in recombinant form, purified, and applied exogenously to susceptible Gram-positive bacteria, lysins cleave highly conserved regions of the bacterial cell wall at specific peptidoglycan bonds that are necessary to maintain structural stability and bacterial viability. Cleavage of the peptidoglycan results in rapid bacteriolysis.

Phage-derived recombinant lysins offer the potential to overcome many of the issues associated with whole phage therapy and may address serious, systemic infections via a novel mechanism of action that is complimentary to conventional antibiotic therapies (Czaplewski and Rex, 2016; Fischetti, 2010).

CF-301 is a novel, recombinantly-produced bacteriophage-derived lysin and has potent activity specific against *Staphylococcus aureus.* It is a novel antibacterial agent in Phase 2 clinical development for systemic administration.

Study CF-301-101, was a Phase 1 study designed to evaluate the safety, tolerability, and pharmacokinetics of single, escalating intravenous (IV) doses of CF-301 in healthy adult males and females. As CF-301 is a therapeutic nonhuman protein, the emergence of an inflammatory response was explored by measuring the a range of inflammatory markers before and after administration of CF-301 or placebo.

Methods

CF-301-101 was a single-center, double-blind, randomized, placebo-controlled, escalating, single dose study in healthy male and female subjects. The study included 4 dosing cohorts (0.04, 0.12, 0.25, and 0.4 mg/kg/dose). Subjects were randomized to either CF-301 (4 subjects) or placebo (2 subjects) per cohort and a 4:2 male/female ratio per dosing cohort was planned. A Data Safety Monitoring Board (DSMB) was established to monitor safety at pre-specified time points throughout the study.

Study drug was administered as a single 2 hour IV infusion and inflammatory markers were assessed to characterize the pro-inflammatory potential of CF-301.

Erythrocyte sedimentation rate (ESR) and high-sensitivity C-reactive protein (hsCRP) samples were obtained before and after dosing (Days 2, 3, 4, 5 , 8 , 14 and 28). Complement factors Bb, C3a, C5a, and CH50 were assessed before dosing and 5 minutes into the infusion, at the end of infusion and at 24 hours. For any subject who experienced infusion reaction symptoms IL-6 and TNF-α were also to be collected.

Results

13 subjects received CF-301 (4 subjects at the 0.04 mg/kg/dose level; 4 subjects at the 0.12 mg/kg/dose level; 4 subjects at the 0.25 mg/kg/dose level; and 1 subject at the 0.4 mg/kg/dose level), and 7 subjects received placebo. Demographics are presented in Table 1. All subjects completed visits through Study Day 28.

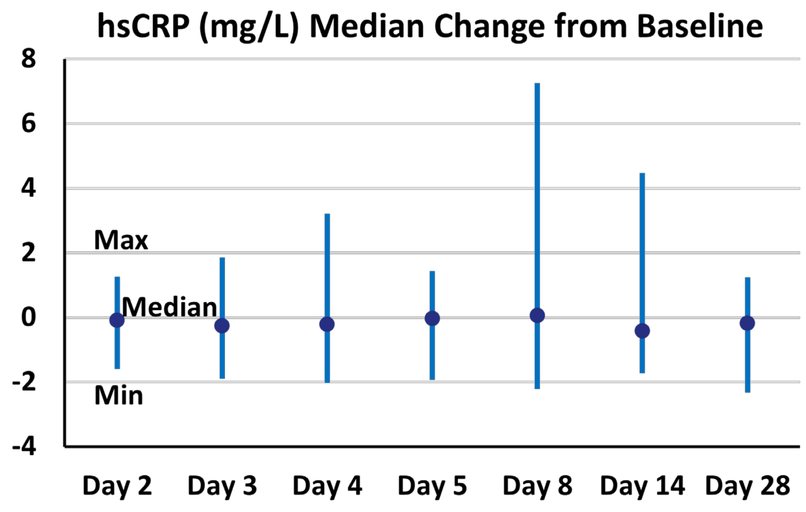
Results

CF-301 was generally safe and well tolerated. There were no serious AEs (SAEs), no discontinuations due to AEs, no AEs due to CF-301-related hypersensitivity, no infusion reactions, and no deaths. Four subjects had at least 1 treatment emergent AE (TEAE) during the study: 2 in the placebo group, 1 in the 0.04 mg/kg/dose CF-301 group, and 1 in the 0.12 mg/kg/dose CF-301 group. All TEAEs were mild in intensity and resolved.

Overall the mean age and standard deviation (SD) of subjects was 33.7 (SD, 13.6) years; 55% were male; 10 were white, 9 black, and one Asian; the mean weight was 74 (SD, 16) kg, and body mass index 24.95 (SD, 3.77) kg/m^2.

hsCRP

Changes from baseline by Day for hsCRP in subjects in the CF-301 group are shown below**.** One subject had a high value at Day 8 with no associated clinical symptoms. The hsCRP in the placebo group showed similar changes.



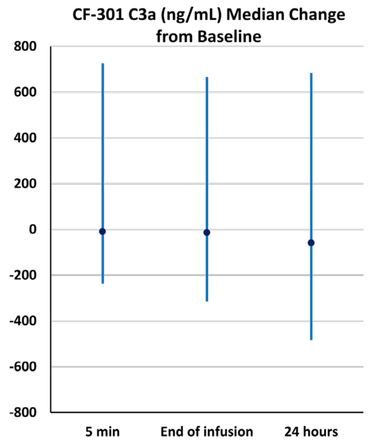
ESR

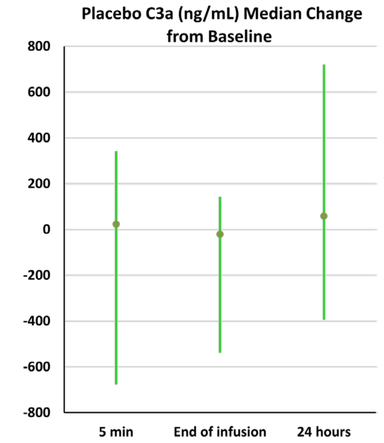
The median ESR ranged from 2 – 4 over through Day 28. And changes from baseline were within a narrow range for all subjects. There were no differences between placebo and CF-301

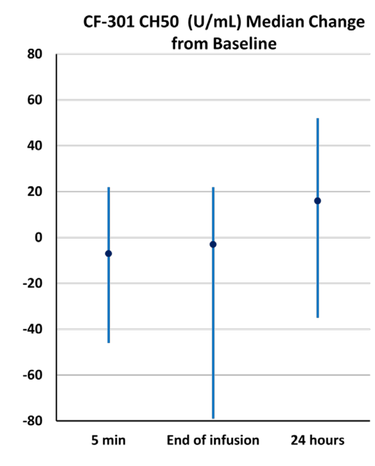
Compliment Components: Bb, C3a, C5a, and CH50

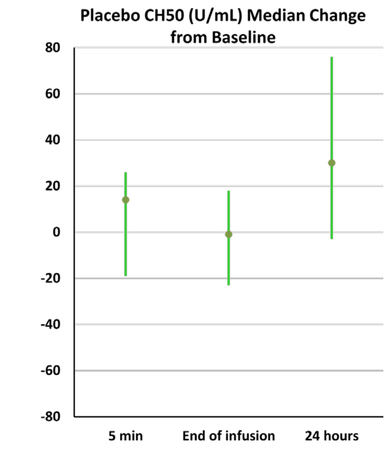
Results were highly variable for Bb, C3a, C5a, and CH50 parameters in all subjects and no clinically significant mean changes from baseline were observed. The values for all complement components were similar between the placebo and CF-301 groups. The changes from baseline by Day for CH50 and C3a for placebo and CF-301 groups are presented in the following 4 graphs.

Results









IL-6 and TNF-α

IL-6 and TNF-α were not collected there were no reported infusion reactions.

Conclusions

- CF-301 was well tolerated, with no clinical adverse safety signals.
- Following a administration of a single IV infusion of CF-301 over 2 hours there were no clinically relevant changes from baseline
  - ESR or hsCRP
  - complement factors Bb, C3a, C5a, and CH50.
- These results suggest that there is a low propensity for a single IV dose of CF-301 0.04 – 0.4 mg/kg to induce an inflammatory response.