A PHASE I STUDY OF STAPHYLOCOCCAL PROTEIN A IN PATIENTS WITH ACTIVE RHEUMATOID ARTHRITIS ON METHOTREXATE

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Background: Staphylococcal protein A (SpA) is a bacterial B cell superantigen that binds with high affinity to the Fc region of most Igs and to the Fab region of Igs in the V_H3 gene family. SpA is active in the mouse collagen-induced arthritis model and proved safe and well-tolerated in a Phase I trial at intravenous doses of up to 1.5 µg /kg. SpA forms multimeric complexes with human antibodies that appear to mediate inhibitory signals via FcR1 receptors on monocyte/macrophages, B-cells, and osteoclasts (1); however, the mode of action of SpA in the treatment of rheumatoid arthritis (RA) is not fully understood.

Objectives: To evaluate the safety, pharmacokinetics, antigenicity, and potential effects on disease activity in patients with active RA, despite methotrexate or leflunomide therapy, in a double-blind placebo-controlled study.

Methods: This multicenter double-blind placebo-control sequential dose-escalation study enrolled 41 seropositive RA patients at 5 centers who met study entry criteria; patients had a mean of 11.5 swollen and 17.3 tender joints (28 joint count). Sequential groups of patients were dosed with 1.5, 3.0, 6.0, or 12.0 µg /kg of highly purified SpA (PRTX-100), or placebo (randomized 3:1), administered as 5 weekly intravenous infusions. Safety and disease activity was monitored over a period of 24 weeks, anti-SpA antibodies were measured at weeks 3, 8, and 24, and PK was assessed after the first and fourth dose.

Results: Study treatments were generally well tolerated. The most common treatment-emergent adverse events were fatigue (20% of patients), headaches (17%), and arthritis flares (34%). No treatment-related SAEs occurred. Two patients discontinued the therapy due to treatment-related AE's. One patient with impaired cardiac function experienced dyspnea, orthopnea, and Hgb desaturation one hour the end of her first infusion, then recovered fully within three hours. Another patient discontinued after a mild asthma exacerbation following the third dose. Two other patients discontinued prior to completing all treatments for unrelated reasons. No clinically significant trends in laboratory values were noted. Mean plasma SpA Cmax after the first

infusion was generally proportional to dose and ranged from 48 ng/mL for 1.5 µg/kg doses to 297 ng/mL for the 12 µg/kg dose. At study day 85, both the 6 mcg dose cohort and 12 mcg cohorts demonstrated reductions of DAS28CRP from means of 4.8 and 5.1 respectively to means < 3.2 (low disease activity) whereas scores for the placebo cohort did not. At Day 85, the DAS28CRP components most changed by active treatment were the swollen joint counts and Patient Global VAS score.

Conclusions: Five weekly doses of SpA demonstrated an acceptable safety profile. Although the number of patient was small, a treatment response is suggested. A delayed peak response of disease activity (4 to 8 weeks after the last dose) may indicate immunomodulatory rather than direct anti-inflammatory activity.

References: 1. Maclellan, L, Montgomery J, Sugiyama F, KitsonS, Thummler K, Silverman G, Beers S, Nibbs R, McInnes I, and Goodyear C. 2011.Co-opting endogenous immunoglobulin for the regulation of inflammation and osteoclastogenesis. Arthritis Rheum. 63(12):2897-3907

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