A Phase 1 Dose-Ranging Repeated-Dose Trial of Parenteral Staphylococcal Protein A (PRTX-100) in Patients with Active Rheumatoid Arthritis on Methotrexate or Leflunomide Therapy

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ABSTRACT

Background: Staphylococcal protein A (SpA) binds with high affinity to the Fc region of human immunoglobulin G and also to the Fab framework region of immunoglobulin encoded from genes of the VH3 family. At intravenous doses up to 1.5 µg/kg weekly SpA was found to have an acceptable safety profile in a Phase I rheumatoid arthritis (RA) trial. The current Phase I study evaluates the safety and effect on RA disease activity of 6 months of SpA treatment.

Methods: This study enrolled 61 RA patients (pts) at 8 US centers. In Part 1 of the study, 41 pts received 5 weekly doses of either placebo, 1.5, 3, 6 or 12 µg/kg of SpA. Partial results from Part 1 have been reported previously [1]. In Part 2, pts received placebo or a fixed SpA dose of either 240 µg or 420 µg given as 5 weekly doses followed by 'maintenance' doses at weeks 8, 12, 16 and 20 (6 months' total treatment). Adverse events (AEs), pharmacokinetics, anti-SpA antibodies and disease activity (ACR20/50/70, DAS28-CRP, and CDAI [Clinical Disease Activity Index]) are being evaluated over the course of this ongoing study.

Results: Twenty pts were randomized in Part 2: 3 pts (240 µg), 12 pts (420 µg) and 5 pts (placebo). All AEs were Grade 1 or 2 in severity with the exception of 1 pt who experienced Grade 3 influenza (unrelated to treatment) and 1 pt with Grade 3 worsening of arthritis (related to treatment). 9 pts (45%) had related AEs, the most common being transient flare of musculoskeletal symptoms usually occurring 1–3 days post-infusion. In Parts 1 and 2 of the study, there were no deaths or serious AEs considered to be related to SpA. Nine of the 12 pts in the 420 µg SpA arm met per-protocol criteria for efficacy evaluation. For comparative purposes, the control group was pooled from the 15 placebo pts enrolled in Parts 1 and 2; 13 placebo pts met per-protocol criteria for efficacy evaluation. Of the 9 pts in Part 2 that received 420 µg SpA, 56% achieved ACR20 at day 113 vs. 31% of pts in the control group. A similar pattern was seen with the ACR50: on day 113, 33% of 9 SpA-treated pts attained an ACR50 vs. 8% of pts in the control group. CDAI data also indicated some reduction in disease activity, as 44% of 420 µg pts achieved a CDAI of ≤14 on 3 or more consecutive visits vs. 23% of pts in the control group. SpA and control pts had MDHAQ mean physical function scores of 3.57 and 3.59, respectively, at baseline. By day 85, the change from baseline was –1.17 and –0.59 for SpA and control pts, respectively. At day 113, the change from baseline was –1.38 vs. –0.6, respectively.

Conclusion: A 6-month regimen of 5 weekly infusions of SpA followed by 4 monthly 'maintenance' infusions had an acceptable safety profile in pts with RA. The most common AEs seemed to be associated with transient worsening of musculoskeletal symptoms. During a 6-month study period, SpA appeared to result in some reduction in disease activity. Some patients experienced improvements.

Reference:
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INTRODUCTION

Staphylococcal protein A (SpA) is a bacterial virulence factor which structurally consists of five homologous immunoglobulin (Ig) binding domains placed in tandem.[1] Each SpA domain is capable of binding with high affinity to the Fc region of human IgG and also binds to the Fab framework region of Igs in the mammalian VH3 gene family.[2] This ability to bind to VH3 Igs results in SpA being one of the best-characterized mammalian B-cell superantigens.

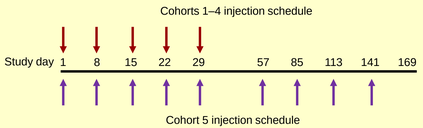
Non-clinical papers suggest that SpA, in the presence of excess serum IgG, may form small complexes of SpA and IgG,[3] which in vitro and in vivo can induce 'alternatively-activated' or 'regulatory' macrophages. These have an anti-inflammatory phenotype, and such complexes may have activity in the mouse collagen-induced arthritis model.[4] SpA also interacts directly with VH3 B-cells in mice and, at doses of 5 or 50 mg/kg, can cause activation followed by apoptosis of VH3-expressing B-cells.[5]

In patients with active rheumatoid arthritis (RA) on methotrexate (MTX), parenteral SpA (PRTX-100) was safe and well-tolerated in a prior phase I trial when given as 4 weekly IV injections at doses up to 1.5 µg/kg; higher doses of PRTX-100 induced delayed, but sustained decreases in RA activity in some patients.[6] In a second phase I trial in patients with active RA on MTX, PRTX-100 was safe and well-tolerated when given as 5 weekly IV injections of doses from 1.5–12 µg/kg and more PRTX-100-treated than placebo-dosed patients had sustained decreases in RA activity.[7]

METHODS

- 41 patients from Cohorts 1–4 were enrolled on study as previously described[7] and shown in Figure 1.
- Cohort 5: 20 patients with ≥4 swollen and ≥5 tender joints on a stable dose of MTX or leflunomide were enrolled. 12 patients were randomized to a fixed dose of 420 µg PRTX-100, 3 patients were randomized to a fixed dose of 240 µg PRTX-100 and 5 patients were randomized to placebo.
- Cohort 5 patients received 5 weekly fixed doses of PRTX-100 followed by 4 monthly maintenance doses at weeks 8, 12, 16, and 20 (Figure 1).
- The primary study endpoint was safety. Safety assessments included adverse events, complete blood count, blood chemistry, urinalysis and electrocardiogram. Pharmacokinetic profiles were determined after dosing on Days 1 and 22.
- The secondary endpoints were immunogenicity and disease activity. Anti-drug antibodies (ADAs) were measured on Days 1, 29, 57, and 169 for Cohort 5.

Figure 1. Schedule of injections



RESULTS

The addition of 4 monthly maintenance doses of PRTX-100 is safe:
- There were no deaths in the study.
- No serious adverse reactions were reported.
- The most common adverse reactions consisted of constitutional symptoms and transient worsening of arthritic manifestations.
- No cases of anaphylaxis were reported.
- Preliminary analyses suggest that the addition of 4 monthly maintenance doses of PRTX-100 in Cohort 5 did not increase the rate of adverse reactions.
- 'Fixed' dosing in Cohort 5 gave similar PK values to 'by weight' dosing in Cohorts 1–4.

Table 1. Adverse reactions occurring in ≥2 patients in Cohorts 1–4 (n=31)

Adverse reaction term	Number
Headache	18
Arthritis	9
Fatigue	9
Nausea	9
Myalgia	7
Dizziness	6
Rheumatoid arthritis	5
Arthralgia	4
Muscle spasm	4
Chills	2
C-reactive protein increased	2
Diarrhea	2
Dyspnea	2
Flushing	2
Infusion-related reaction	2
Musculoskeletal pain	2
Pyrexia	2
Rash	2
Urinary tract infection	2

Table 2. Adverse reactions in Cohort 5 (n=20)

Adverse reaction term	Number
Arthritis (worsening)	3
Arthralgia	2
Chills	1
Influenza-like illness	1
Injection site joint pain	1
Pyrexia	1
Lip swelling	1
Myalgia	1
Rheumatoid arthritis	1
Paresthesia	1
Tremor	1
Pruritus	1
Peripheral coldness	1
Total reaction terms	16

Table 3. Summary (mean ± SD) of pharmacokinetic parameters for PRTX-100 after a 20-minute IV infusion of 240 µg and 420 µg PRTX-100 once weekly to patients with active RA

	PRTX-100 dose		
Parameters[a]	240 µg	420 µg	6 µg/kg
Day 1			
C_{max}, ng/mL	77.3 ± 42.7 (3)	144 ± 44.6 (10)	158 ± 22.3 (18)
T_{max}, h	0.38 (3) [0.00–0.58]	0.48 (10) [0.38–1.08]	0.50 (18) [0.32–1.08]
Day 22			
C_{max}, ng/mL	47.4 ± 37.6 (3)	114 ± 41.2 (8)	109 ± 42.1 (16)
T_{max}, h	0.38 (3) [0.38–0.58]	0.38 (8) [0.38–0.58]	0.5 (16) [0.17–1.05]

[a]Arithmetic mean ± standard deviation (N) except T_{max} for which the median (N) [range] is reported.

Table 4A. The addition of 4 monthly maintenance doses of PRTX-100 does not significantly change the percentage of patients with IgG ADAs

	Number of patients positive for IgG ADA					
Treatment	PRTX-100	PRTX-100	PRTX-100	PRTX-100	PRTX-100	Placebo
Dose	240 µg	420 µg	240 µg and 420 µg	Cohorts 1–4	All	All
No. of subjects	3	12	15	31	46	15
Day 22 / 29 [1]	2 / 3 (66.7%)	7 / 8 (87.5%)	9 / 11 (81.8%)	19 / 27 (70.3%)	28 / 38 (73.7%)	0 / 13
Day 57	1 / 2 (50.0%)	5 / 7 (71.4%)	6 / 9 (66.7%)	19 / 28 (67.9%)	25 / 37 (67.6%)	0 / 13
Day 169 [2]	2 / 3 (66.7%)	7 / 11 (63.6%)	9 / 14 (64.3%)	15 / 26 (57.7%)	24 / 40 (60.0%)	0 / 12

[1] Day 22 was used for Cohorts 1–4 and Day 29 was used for Cohort 5 (240 µg and 420 µg doses).
[2] By Day 169 subjects in Cohort 5 had received 4 additional monthly maintenance doses of PRTX-100.

Table 4B. The addition of 4 monthly maintenance doses of PRTX-100 does not significantly change the percentage of patients with IgE ADAs

	IgE ADAs			
Treatment	PRTX-100	PRTX-100	PRTX-100	Placebo
Cohort	Cohort 5	Cohorts 1–4	All	All
Day 22, 57, 169	0 / 14	5 / 30 (16.7%)	5 / 44 (11.2%)	0 / 13

- No patients with detectable IgE antibodies had respiratory problems or anaphylaxis.
- The 5 patients with IgE ADA were treated with 1.5 µg/kg (1), 3 µg/kg (1), 6 µg/kg (1), and 12 µg/kg (2).
- The 5 patients deemed positive for IgE ADAs showed IgE levels slightly above the lower limit of detection for the assay (3 ng/mL), with values ranging from 3.2 to 7.0 ng/mL.
- Assay performed in the laboratory of Robert G Hamilton, PhD, D ABMLI, Professor of Medicine and Pathology, Johns Hopkins University School of Medicine, and Director, Johns Hopkins Dermatology, Allergy and Clinical Immunology Reference Laboratory.

Table 4C. Cohort 5 patients tended to have higher ADA titers on Day 169

	Treatment	
Summary	PRTX-100 Cohorts 1–4	PRTX-100 Cohort 5
No. of subjects [1]	31	15
Day 22/Day 29 [2]		
N	19	9
Mean (SD)	1373.7 (2314.11)	4646.1 (6695.84)
Median	622.0	2151.0
Day 57		
N	18	5
Mean (SD)	1903.8 (3354.85)	1882.2 (686.56)
Median	515.0	2183.0
Day 169		
N	14	8
Mean (SD)	839.6 (1228.27)	2409.1 (2475.49)
Median	314.5	1735.0

[1] Intent to treat subjects.
[2] Day 22 was used for Cohorts 1–4 and Day 29 was used for Cohort 5 (240 µg and 420 µg doses).

Table 4D. The presence of ADAs does not preclude an ACR20 response to PRTX-100 on Day 57 or Day 169

	Treatment					
	PRTX-100 Cohorts 1–4 (n=31)		PRTX-100 Cohort 5 (n=15)		PRTX-100 All Cohorts (n=46)	
Summary	Antibody Positive	Antibody Negative	Antibody Positive	Antibody Negative	Antibody Positive	Antibody Negative
ACR20						
Day 57	9 / 18 (50.0%)	4 / 9 (44.4%)	4 / 6 (66.7%)	1 / 2 (50.0%)	13 / 24 (54.2%)	5 / 11 (45.5%)
Day 169	6 / 15 (40.0%)	4 / 11 (36.4%)	3 / 5 (60.0%)	3 / 5 (60.0%)	9 / 20 (45.0%)	7 / 16 (43.8%)

Table 5. Disease activity measurements during PRTX-100 treatment

	PRTX-100 dose				
	240 µg	420 µg	PRTX-100 Cohorts 1-4	PRTX-100 All	Placebo All
No. of subjects [1]	3	9	29	41	15
Day 57 ACR20	2 / 3 (66.7%)	4 / 8 (50.0%)	14 / 28 (50.0%)	20 / 39 (51.3%)	5 / 13 (38.5%)
Day 57 ACR50	0 / 3	1 / 9 (11.1%)	8 / 27 (29.6%)	9 / 39 (23.1%)	2 / 13 (15.4%)
Day 57 ACR70	0 / 3	1 / 9 (11.1%)	3 / 28 (10.7%)	4 / 40 (10.0%)	0 / 12
ACR20					
Day 15	1 / 3 (33.3%)	3 / 8 (37.5%)	6 / 28 (21.4%)	10 / 39 (25.6%)	4 / 13 (30.8%)
Day 29	2 / 3 (66.7%)	4 / 8 (50.0%)	8 / 28 (28.6%)	14 / 39 (35.9%)	4 / 13 (30.8%)
Day 57	2 / 3 (66.7%)	4 / 8 (50.0%)	14 / 28 (50.0%)	20 / 39 (51.3%)	5 / 13 (38.5%)
Day 85	1 / 1 (100%)	5 / 9 (55.6%)	14 / 29 (48.3%)	20 / 39 (51.3%)	4 / 10 (40.0%)
Day 113	2 / 3 (66.7%)	5 / 7 (71.4%)	10 / 25 (40%)	17 / 35 (48.6%)	4 / 11 (36.4%)
Day 169	1 / 2 (50.0%)	5 / 6 (83.3%)	7 / 22 (31.8%)	13 / 30 (43.3%)	5 / 8 (62.5%)

[1] Intent to treat subjects.
[2] Four doses for Cohorts 1–4: 1.5 µg/kg, 3 µg/kg, 6 µg/kg, and 12 µg/kg.

Table 6. Using Vectra DA scores on patient screen improves trial efficacy outcome (Cohort 1–4 analysis)

	% of patients with ACR response by CRP criteria			
Baseline values	ACR20	ACR50	ACR70	No response
Treated CRP ≥3 [1]	5 / 12 (41.7%)	4 / 12 (33.3%)	1 / 12 (8.3%)	7 / 12 (58.3%)
Treated CRP <3	9 / 16 (56.35)	4 / 16 (25.0%)	2 / 16 (12.5%)	7 / 16 (43.8%)
Placebo ≥3	2 / 6 (33.3%)	0 / 6	0 / 6	4 / 6 (66.7%)
Placebo <3	0 / 2	1 / 2 (50.0%)	0 / 2	1 / 2 (50.0%)

	% of patients with ACR response by Vectra DA criteria [2]			
Baseline values	ACR20	ACR50	ACR70	No response
Treated Vectra DA ≥30	12 / 18 (66.7%)	7 / 18 (38.9%)	2 / 18 (11.1%)	6 / 18 (33.3%)
Treated Vectra DA <30	0	0	0	3 / 3 (100%)
Placebo Vectra DA ≥30	3 / 6 (50.0%)	0	0	3 / 6 (50.0%)

[1] CRP in mg/L.
[2] Not all patients had samples for Vectra DA analyses.

DISCUSSION

The addition of 4 fixed monthly maintenance doses of PRTX-100 to an initial regimen of 5 fixed weekly doses of PRTX-100 did not change the rate or type of adverse events.

The most common adverse reactions consisted of constitutional symptoms and transient worsening of arthritis manifestations. All adverse events were Grade 1 or 2 in severity with the exception of 1 patient who experienced Grade 3 influenza (unrelated to treatment) and 1 patient with Grade 3 worsening of arthritis (related to treatment). There have been no cases of anaphylaxis.

PRTX-100 appears to be well tolerated in all patients, even those who develop ADAs. As PRTX-100 is a foreign protein, it might be expected that individuals will develop ADAs, but thus far there appears to be no correlation between the development of ADAs and treatment response.

There are more ACR20 responders at later timepoints for patients in Cohort 5 who received the additional 4 monthly maintenance doses of PRTX-100 than patients in Cohorts 1–4.

These preliminary analyses suggest the addition of monthly maintenance doses of PRTX-100 may reduce disease activity.

Using Crescendo Bioscience's Vectra DA as entry criteria in post-hoc analysis of Cohorts 1–4 allowed detection of patients who had been entered into the study with very low disease activity (Vectra DA scores of 12, 19, and 21), despite having DAS-28 CRP scores above 5. Analyses of data with these patients removed improved the endpoint analysis for ACR20, ACR50, and ACR70 for Cohorts 1–4.

CONCLUSIONS

- A 6-month regimen of 5 weekly infusions of PRTX-100 followed by 4 monthly maintenance infusions had an acceptable safety profile in patients with RA. The most common adverse events appeared to be associated with transient worsening of musculoskeletal symptoms.
- The addition of 4 monthly maintenance doses of PRTX-100 does not increase the rate or type of adverse events.
- Fixed dosing of PRTX-100 and the addition of 4 monthly maintenance doses did not increase the percentage of patients developing ADAs.
- Despite most patients developing ADAs, presence of ADAs does not appear to preclude improvement in RA disease measurements with PRTX-100.
- Adding the criteria of a Vectra DA baseline measurement >30 at study entry for an RA trial allows for a non-subjective measurement of disease activity and led to improved endpoint efficacy measurements with PRTX-100 in the current study.

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