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Safety and Tolerability of Bacteriophage Therapy for Chronic Rhinosinusitis Due to *Staphylococcus aureus*

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IMPORTANCE *Staphylococcus aureus* infections are associated with recalcitrant chronic rhinosinusitis (CRS). The emerging threat of multidrug-resistant *S aureus* infections has revived interest in bacteriophage (phage) therapy.

OBJECTIVE To investigate the safety, tolerability, and preliminary efficacy of ascending multiple intranasal doses of investigational phage cocktail AB-SA01 in patients with recalcitrant CRS due to *S aureus*.

DESIGN, SETTING, AND PARTICIPANTS This phase 1, first-in-humans, open-label clinical trial of multiple ascending doses was conducted at a single tertiary referral center from December 1, 2015, through September 30, 2016, with follow-up completed on December 31, 2016. Patients with recalcitrant CRS (aged 18-70 years) in whom surgical and medical treatment had failed and who had positive *S aureus* cultures sensitive to AB-SA01 were recruited. Findings were analyzed from February 2 through August 31, 2017.

INTERVENTIONS Three patient cohorts (3 patients/cohort) received serial doses of twice-daily intranasal irrigations with AB-SA01 at a concentration of 3×10^8 plaque-forming units (PFU) for 7 days (cohort 1), 3×10^8 PFU for 14 days (cohort 2), and 3×10^9 PFU for 14 days (cohort 3).

MAIN OUTCOMES AND MEASURES The primary study outcome was the safety and tolerability of intranasal AB-SA01. Safety observations included vital signs, physical examinations, clinical laboratory test results, and adverse events. The secondary outcome was preliminary efficacy assessed by comparing pretreatment and posttreatment microbiology results, disease-relevant endoscopic Lund-Kennedy Scores, and symptom scores using a visual analog scale and Sino-Nasal Outcome Test–22.

RESULTS All 9 participants (4 men and 5 women; median age, 45 years [interquartile range, 41.0-71.5 years]) completed the trial. Intranasal phage treatment was well tolerated, with no serious adverse events or deaths reported in any of the 3 cohorts. No change in vital signs occurred before and 0.5 and 2.0 hours after administration of AB-SA01 and at the exit visit. No changes in biochemistry were found except for 1 participant in cohort 3 who showed a decrease in blood bicarbonate levels on exit visit, with normal results of physical examination and vital signs. All biochemistry values were normalized 8 days later. No changes in temperature were recorded before, during, or after treatment. Six adverse effects were reported in 6 participants; all were classified as mild treatment-emergent adverse effects and resolved by the end of the study. Preliminary efficacy results indicated favorable outcomes across all cohorts, with 2 of 9 patients showing clinical and microbiological evidence of eradication of infection.

CONCLUSIONS AND RELEVANCE Intranasal irrigation with AB-SA01 of doses to 3×10^9 PFU for 14 days was safe and well tolerated, with promising preliminary efficacy observations. Phage therapy could be an alternative to antibiotics for patients with CRS.

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Supplemental content

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The management of recalcitrant chronic rhinosinusitis (CRS) is increasingly challenged by infections with difficult-to-treat biofilms and multidrug-resistant bacteria. Antibiotics can alleviate symptoms in acute exacerbations of recalcitrant CRS but fail to eradicate the biofilm nidus, resulting in a relapsing course of disease.[1] Among patients with recalcitrant CRS and failed surgical intervention, as many as 50% of biofilms identified are dominated by *Staphylococcus aureus*.[2] With a growing prevalence of resistance to first-line antibiotics and lack of research and development of new antibiotics, novel antibiofilm agents are needed to help control disease in these patients.

Bacteriophage (phage) therapy was proposed as an antibacterial treatment as early as the 1910s. Increasing interest in its potential to treat bacterial infections has been recently driven by the exponential increase of antibiotic-resistant strains.[3] Phages are viruses that infect only 1 or a few closely related bacterial species with no pathogenic effect on mammalian cells. Phages can be divided into obligately lytic and temperate (also called lysogenic) phages.[4,5] Lytic phages hijack the bacterial host cellular machinery to produce progeny phages, kill the bacteria to reenter the surrounding environment, and proceed to invade new bacterial hosts. Temperate phages integrate their genome into the host genome and remain dormant, benignly replicating with the bacteria until triggered to enter the lytic cycle. Phage therapy uses obligately lytic phages to achieve maximal bacterial elimination and minimize the risks for horizontal gene transfer.[6,7]

Phage therapy offers several potential advantages over oral antibiotics.[8] For example, biofilms are more effectively removed by phages[9] but are more resistant to antibiotics to 1000-fold.[10] Phages offer a highly specific, targeted treatment that is expected to cause less disruption of the normal microbiota than broad-spectrum antibiotics, resulting in fewer systemic adverse effects. Phages self-replicate at the site of infection, reducing the need for frequent administration. Phages can be effective against antibiotic-resistant strains such as methicillin-resistant *S aureus* and have the potential to alter the resistance profile of antibiotic-resistant strains.[11,12]

The phage cocktail used in the present study, AB-SA01, is an equipotent mixture of 3 natural lytic phages that belong to the *Myoviridae* family. The AB-SA01 component phages are obligately lytic, are incapable of specialized transduction, contain no known antibiotic resistance or bacterial virulence genes, and are capable of killing a wide range of clinical *S aureus* strains.[13] Related phages demonstrated short-term[14] and long-term[15] safety and efficacy in an established sheep *S aureus* biofilm sinusitis model.

As with antibiotics, *S aureus* can develop resistance against phages, resulting in bacteriophage insensitive mutants.[1] A few in vitro studies have shown anti-*S aureus* phage mixes were superior to single phages because they reduce the risk of developing bacteriophage-insensitive mutants[16,17] and provide a wider host range effect.[18]

Designing and executing robust clinical trials is key to building a greater understanding of the short- and long-term clinical effects of phage therapy and required for licensure. The purpose of this first-in-human, open-label study was to determine the safety and tolerability of intranasal application of the phage cocktail AB-SA01 in patients with recalcitrant CRS due to *S aureus*. In addition, we determined the feasibility of our trial protocol, including preliminary efficacy assessments.

Key Points

Question What are the systematic safety and efficacy data necessary to incorporate bacteriophage therapy as a clinical alternative to antibiotics?

Findings This first-in-humans, phase 1 trial aimed to investigate the safety, tolerability, and preliminary efficacy of the ascending dose intranasal phage cocktail AB-SA01 in 9 patients with recalcitrant chronic rhinosinusitis positive for *Staphylococcus aureus*. Intranasal AB-SA01 was safe and well tolerated to doses of 3×10^9 plaque-forming units for 14 days, and 2 of 9 patients had eradication of infection.

Meaning Intranasal irrigation with phage cocktail AB-SA01 is safe and well tolerated at the highest study dose with promising preliminary efficacy results and could be a potential alternative to antibiotics for patients with chronic rhinosinusitis due to *S aureus*.

Methods

Participants and Study Design

Ethics approval was granted by the Central Northern Adelaide Health Service Human Research Ethics Committee to conduct the trial within its network of teaching hospitals in Adelaide, Australia. All participants gave written informed consent in accordance with the Declaration of Helsinki. The protocol inclusion and exclusion criteria are outlined in eTable 1 in Supplement 1. Patients aged 18 to 70 years who gave informed consent, were able to comply with the trial protocol, and previously underwent endoscopic sinus surgery were included in the study if they presented with an *S aureus* sinus infection sensitive to AB-SA01. Because these participants had recalcitrant CRS with a history of endoscopic sinus surgery, they received routine twice-daily saline irrigations before study entry.

This prospective, open-label, phase 1 clinical trial was conducted at a single tertiary referral center from December 1, 2015, through September 30, 2016, with follow-up completed on December 31, 2016 (the trial protocol is found in Supplement 2); findings were analyzed from February 2 through August 31, 2017. Each cohort received serial doses of AB-SA01 intranasal irrigations in the following ascending dosage regimens: twice-daily intranasal irrigations of AB-SA01 at a concentration of 3×10^8 plaque-forming units (PFU) for 7 days (cohort 1), 3×10^8 PFU for 14 days (cohort 2), or 3×10^9 PFU for 14 days (cohort 3).

In cohort 1, all 3 participants received serial doses only after successful completion of a safety and tolerability assessment by a safety medical committee. Once treatment in cohort 1 was completed, the safety data were reviewed by the safety medical committee before treatment in cohort 2 was commenced. After the sentinel participant from cohort 2 was treated without safety concerns, the remaining 2 participants in cohort 2 received treatment in parallel. The use of a sentinel participant was then repeated for cohort 3 (**Figure 1**).

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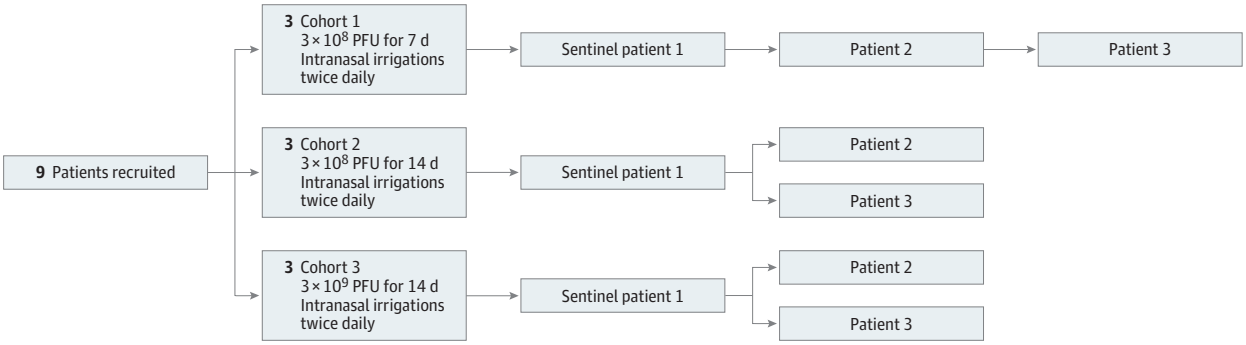
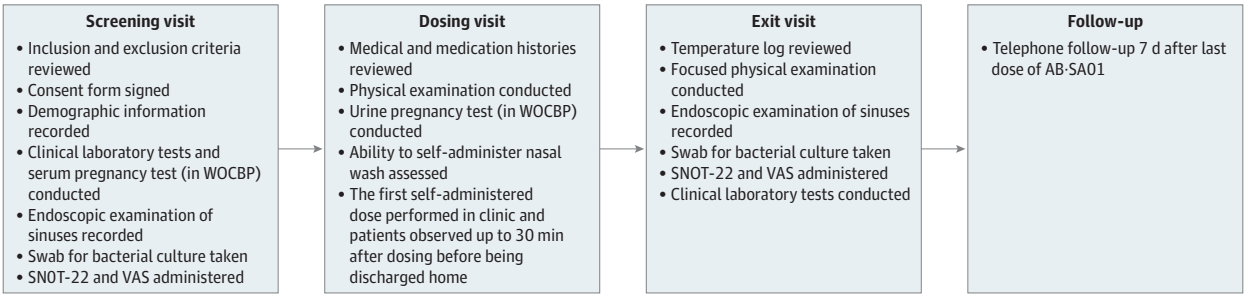
Figure 1. Flow Diagram Describing Participant Flow and Specific Administered Treatments



PFU indicates plaque-forming units.

Figure 2. Flow Diagram Describing Detailed Trial Protocol at All Points of the Study



SNOT-22 indicates Sino-Nasal Outcome Test–22; VAS, visual analog scale; and WOCBP, women of child-bearing potential.

Sensitivity of *S aureus* Clinical Isolates to AB-SA01

Patient *S aureus* cultures from nasal swabs were streaked on a 1% nutrient agar plate and grown overnight at 37 °C. Colonies were picked using a sterile 1-µL loop and transferred to 3 mL of nutrient broth followed by incubation with shaking (180 rpm) at 37 °C for 16 to 18 hours. Phage sensitivity, defined as productive bacteriophage infection as demonstrated by the presence of individual phage plaques, was determined in triplicates using the soft agar overlay technique as described previously.[3,18] ATCC 25923 was obtained from the American Type Culture Collection and used as a positive control in the assay.[18] Only patients carrying a clinical isolate that was sensitive to AB-SA01 were eligible to be in the study.

Instructions to Prepare the Intranasal Sinus Lavage

Supplies of trial products given to participants are detailed in eTable 2 in Supplement 1. Investigational bacteriophage product AB-SA01 was produced under phase-appropriate Good Manufacturing Practices and supplied by AmpliPhi Biosciences Corporation.

The AB-SA01 vials were stored away from light and in the refrigerator. Prior to use, participants were asked to fill a rinse bottle (NeilMed Pharmaceuticals) with 240 mL of Mount Franklin Spring Water (Coca-Cola Amatil Pty Ltd) and add the proprietary buffered salts sachets (pharmaceutical-grade sodium chloride and sodium bicarbonate), followed by 1 mL of AB-SA01. Participants performed nasal irrigations twice daily, using a new bottle to deliver each dose. All participants had to return all used or unused phage vials to the clinical trial unit at the exit visit to be cross-checked to ensure treatment adherence. Study protocol detailing screening visit, dosing visit, exit visit, and follow up (via telephone 7 days after exit visit) is described in **Figure 2**.

Outcome Measurements for Safety

Biochemistry, Laboratory, and Temperature Measurements

A panel of clinical biochemistry tests was conducted at the screening and exit visits. Levels of hemoglobin, hematocrit, erythrocytes, platelets, and leukocytes (including eosinophils, neutrophils, basophils, lymphocytes, and reticulocytes) were included in hematology measures. Serum levels of urea nitrogen, creatinine, total bilirubin, direct bilirubin, urate, albumin, alkaline phosphatase, creatine kinase, aspartate aminotransferase, alanine aminotransferase, glucose, and bicarbonate were measured. Participants were asked to self-monitor temperature twice daily at home and complete a temperature log throughout the duration of the trial to be handed in at the exit visit.

Concomitant Medications

All medications taken during 30 days before screening and during the trial were recorded and reviewed. Participants using

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Table. Baseline Patient Demographics and Clinical Characteristics

Characteristic	Study Cohort[a]		
	Cohort 1	Cohort 2	Cohort 3
Age, y	55 (52-58)	50 (39-69)	58 (37-69)
Male, No. (%)	1 (33)	0 (0)	3 (100)
History of polyposis, No. (%)	1 (33)	1 (33)	2 (67)
Frontal drill-outs, No. (%)	1 (33)	2 (67)	2 (67)
VAS score[b]	6014 (36.57-78.14)	33.76 (20.14-49.00)	29.62 (18.14-46.71)
SNOT-22 score[c]	72 (45-95)	29 (26-34)	32 (8-70)
Lund-Kennedy Score[d]	11 (8-13)	6 (4-7)	7 (6-8)

Abbreviations: SNOT-22, Sino-Nasal Outcome Test–22; VAS, visual analog scale.

[a] Unless otherwise indicated, data are expressed as median (interquartile range).

[b] Scores range from 0 to 100, with higher scores indicating worse symptoms.

[c] Scores range from 0 to 110, with higher scores indicating worse symptoms.

[d] Scores range from 0 to 20, with higher scores indicating worse endoscopic disease.

routine intranasal corticosteroids on enrollment were instructed to continue this therapy throughout the duration of the study, with at least 2 hours between application of the investigational drug and intranasal corticosteroids.

Clinical Examination and Adverse Events

A general physical examination including vital signs (body temperature, heart rate, respiratory rate, and blood pressure) was conducted at each dosing visit (before and 0.5 and 2.0 hours after dosing) and at the exit visit. Participants were assessed for adverse events coded using the Medical Dictionary for Regulatory Activities, version 2.1, for the duration of the study during clinic visits and at follow-up.

Outcome Measurements for Efficacy

Preliminary efficacy was evaluated by the semiquantitative assessment of pretreatment and posttreatment bacterial cultures. Culture swabs of mucopus visualized from sinus ostia or within sinuses were taken under direct endoscopic guidance.

All patients completed a symptoms score questionnaire at every visit, using Sino-Nasal Outcome Test-22 (SNOT-22)[19] (22 items, each scored from 0-5; total score range, 0-110, with higher scores indicating worse symptoms) and a visual analog scale (VAS)[20] (mean of 6 items scored from 0-100; total score range, 0-100, with higher scores indicating worse symptoms). All patients also had entry and exit endoscopic videos recorded and scored by an independent blinded surgeon (L.M.-V.) using the Lund-Kennedy Score (LKS)[19,21] (score range, 0-20, with higher scores indicating worse endoscopic disease).

Results

A total of 9 patients completed the study (4 men and 5 women; median age, 45 years [interquartile range, 41.0-71.5 years]). Baseline demographic and clinical characteristics are shown in the **Table**. This study from December 2015 to September 2016 involved a total of 28 patients who gave written informed consent, of whom 19 were excluded because of negative bacterial cultures (n = 4), positive bacterial cultures with no *S aureus* growth (n = 9), cultures positive for *S aureus* but insensitive to AB-SA01 (n = 3), and study withdrawal before first treatment (n = 3). The sensitivity of *S aureus* CRS isolates to AB-SA01 was 80% (12 of 15 isolates).

Tolerability, Adverse Effects, and Compliance

All 9 participants were adherent to the treatment protocol and completed the trial, indicating the irrigations were well tolerated, which validated the feasibility of administration route and trial design. No serious adverse effects or deaths occurred, and no adverse effect led to withdrawal of study drug treatment or discontinuation from the study. A total of 6 adverse effects were reported in 6 participants, all of which were classified as treatment-emergent adverse effects (TEAEs). All TEAEs were of mild severity and resolved by the end of the study. One TEAE was reported in 1 of the 3 participants in cohort 1 (diarrhea). Three TEAEs were reported in 2 of 3 participants in cohort 2 (epistaxis, oropharyngeal pain, and cough). Two TEAEs were reported in 2 of the 3 participants in cohort 3 (rhinalgia and decreased blood bicarbonate level). Details of adverse effects reported are listed in eTable 3 in Supplement 1.

Safety Outcomes

No change in vital signs occurred before and 0.5 and 2.0 hours after administration of AB-SA01 and at the exit visit. No changes in biochemistry were found except for 1 participant in cohort 3 who showed a decrease in blood bicarbonate levels on exit visit with normal results of physical examination and vital signs. All biochemistry values were normalized 8 days later. No changes in temperature were recorded before, during, or after treatment.

Preliminary Efficacy Outcomes

Our data describe observed trends, and no statistical analysis was performed owing to the small sample size. All patients had reduction in *S aureus* growth, and 2 of 9 patients had negative cultures after treatment. Data are summarized in eTable 4 in Supplement 1.

Reduced VAS scores were found in cohorts 1 (mean difference, −11.71) and 3 (mean difference, −6.25) after treatment (**Figure 3**A and eTable 5 in Supplement 1). Cohort 2 demonstrated paradoxical worsening in VAS scores (mean difference, 4.81) after treatment, primarily due to a single patient (eFigure in Supplement 1).

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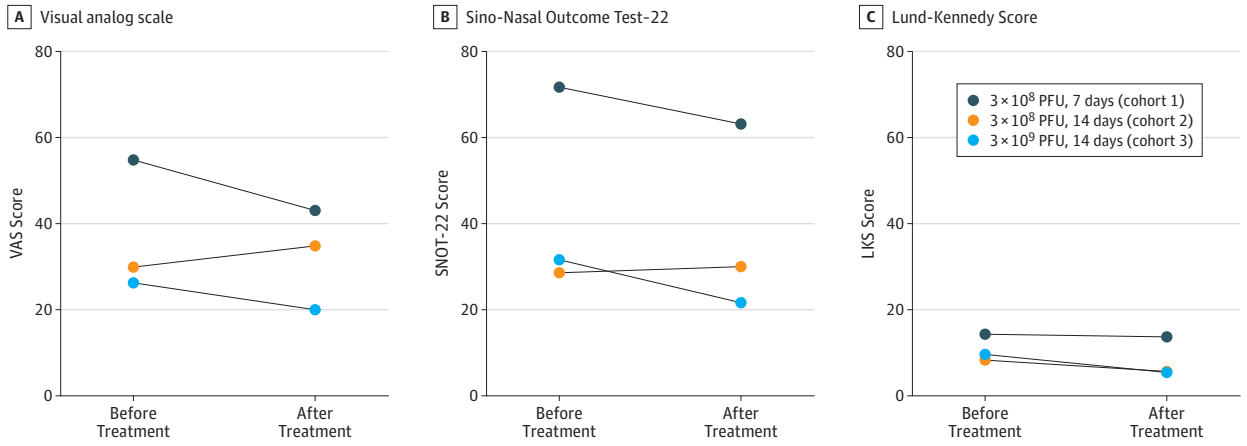
Figure 3. Line Graph of Median Values Before and After AB-SA01 Treatment Across All Cohorts



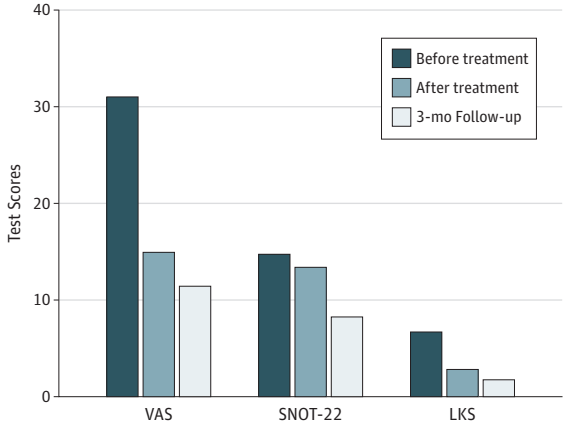
For the Lund-Kennedy Score (LKS), scores range from 0 to 20, with higher scores indicating worse endoscopic disease; Sino-Nasal Outcome Test–22 (SNOT-22), scores range from 0 to 110, with higher scores indicating worse symptoms; and visual analog scale (VAS), scores range from 0 to 100, with higher scores indicating worse symptoms. PFU indicates plaque-forming units.

The SNOT-22 scores were reduced in cohorts 1 (mean difference, −8.4) and 3 (mean difference, −10) after treatment (Figure 3B and eTable 5 in Supplement 1). Cohort 2 demonstrated slightly worse scores (mean difference, 1.3) after treatment. Three of the 9 patients had a minimally clinically important difference (>9)[22] in their SNOT-22 scores (2 from cohort 1, both with an improvement of 9 points; 1 from cohort 1, with an improvement of 16 points). A consistent trend showed improvement in endoscopic LKS across all cohorts (cohort 1: mean difference, −0.6; cohort 2: mean difference, −2.6), with greatest improvement noted in cohort 3 (mean difference, −4.4) (Figure 3C and eTable 5 in Supplement 1).

3-Month Follow-up

Patients who concluded the study with persistence of more than 2 symptoms (nasal discharge, postnasal drip, nasal obstruction, facial pain or pressure, and/or reduced sense of smell) with corresponding endoscopic evidence of pus after 7 days from the last phage treatment dose were then given the option of current, standard, culture-directed oral antibiotic therapy. Five patients received further antibacterial treatment after cessation of the study, and 4 did not. These 4 patients (1 from cohort 1, 2 with *S aureus* eradication from cohort 2, and 1 from cohort 3) were followed up at 3 months with VAS, SNOT-22, and LKS assessments. A continuing trend toward further improvement in all outcome measures was noted. Mean difference in VAS was −3.67 (SD), in SNOT-22 was −5.25 (SD), and in LKS was −1 (SD), in which positive values indicate deterioration from pretreatment and negative values, improvement from pretreatment. Results are shown in **Figure 4**.

Figure 4. Three-Month Follow-up Data



For the Lund-Kennedy Score (LKS), scores range from 0 to 20, with higher scores indicating worse endoscopic disease; Sino-Nasal Outcome Test–22 (SNOT-22), scores range from 0 to 110, with higher scores indicating worse symptoms; and visual analog scale (VAS), scores range from 0 to 100, with higher scores indicating worse symptoms.

Discussion

This study indicated that twice-daily intranasal irrigations to 3×10^9 PFU for 14 days were safe and well tolerated with no serious adverse events. Being a first-in-humans trial, our single-center, open-label phase 1 study was designed to determine the safety and tolerability of ascending concentrations of phage AB-SA01 delivered as an intranasal rinse. Patients selected for this phase 1 study had failed all other conventional medical therapies and therefore served as their own controls. The results of our phase 1 study will guide a phase 2 trial in which a randomized, double-blind, placebo-controlled group will be used to evaluate efficacy.

Our safety result is consistent with the current body of literature with regard to phage use. Several phase 1 human clinical trials have been conducted after application of phages topically (to the skin) or orally, with no serious adverse events reported. In a placebo-controlled phase 1 study,[23] 42 patients

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tested the safety of phage mixes against *S aureus*, *Pseudomonas aeruginosa,* and *Escherichia coli* for the treatment of chronic venous leg ulcers. Patients were treated for 12 weeks and followed up to 24 weeks with no reported significant adverse effects. Another phase 1 study[24] applied a single-spray phage cocktail active against *P aeruginosa* and *S aureus* on colonized burn wounds in 9 patients. No adverse events, clinical abnormalities, or changes in laboratory results were observed. The first modern, double-blinded, controlled clinical trial[25] using phages to treat refractory *P aeruginosa* ear infections was conducted in England in 2007. Twenty-four patients were randomized to receive a single dose of phage or placebo, and both groups were monitored for 42 days. *Pseudomonas aeruginosa* counts were lower for the phage-treated group, with no reported adverse events.

The safety of phage treatment has also been recorded in healthy adults after oral administration. A pilot study[26] tested the safety of a coliphage in 15 healthy adult volunteers. Two different doses of the T4 coliphage (10^3 and 10^5 PFU/mL) were mixed with drinking water. The counts of normal *E coli* flora did not decrease, and no adverse events were reported. In a follow-up study,[27] 15 healthy adults received a phage cocktail composed of 9 *E coli* phages at 2 different concentrations to 3×10^9 PFU. The results showed no adverse events by self-report or clinical examination. The laboratory tests for liver, kidney, and hematology function were also reported as within reference limits. Importantly, oral phage treatment had no effect on the fecal microbiota composition.

Phage preparations administered to humans with CRS have been reported previously,[28,29] with favorable outcomes of approximately 78% to 83% efficacy in infection control and no significant adverse effects. Mills[28] administered α-lysate with occasional β-lysate staphylococcus bacteriophages via a nebulizer for individualized durations followed by monthly maintenance doses. Weber-Dabrowska et al[29] administered phages orally and topically from repeated antral punctures for 4 to 12 weeks. However, the overall interpretation of the aggregate data is limited by the absence of preestablished safety and efficacy end points and information on concomitant antimicrobial therapies.

Limitations

We are only able to comment on the trends observed in this study. The preliminary efficacy observations are promising. Although no clinically meaningful changes occurred in the validated symptom scores relevant to sinus disease (VAS and SNOT-22 scores), the clinical improvements seen endoscopically may be explained by a reduction in bacterial load and the suspected anti-inflammatory effects of phages. In the context of infection, phages have been reported to show anti-inflammatory effects by reducing neutrophils and proinflammatory cytokines, such as interleukin 6 and interleukin 1β,[30,31] and by reducing reactive oxygen species production.[32]

The paradoxical worsening of VAS scores observed in cohort 2 wherein 2 of 3 patients had eradication of bacteria is primarily due to a single patient (eFigure in Supplement 1). Patients 2 and 3 with eradication of bacteria showed consistent improvement across VAS, SNOT-22, and LKS assessments. The reason for patient 1's seemingly paradoxical result is unclear. Inflammation after bacterial lysis and endotoxin release[33] has been a postulated adverse effect, although several studies of phage therapy in humans[34,35] and animals[36,37] did not report any evidence of such responses.

Interestingly, continued clinical observations of certain patients beyond the formal duration of the trial showed a possible sustained clinical effect to 3 months after phage treatment. This finding may be due to the persistence and prophylactic potential of phages, which was not assayed. Future clinical studies may benefit from longer follow-up. Previous in vivo studies[14] have identified low levels of active phages still present within sinuses 24 hours after administration, consistent with various other studies showing serum phage persistence from 48 hours to 38 days after inoculation,[38,39] with clearance of phages by the reticuloendothelial system.[40] The intranasal administration of phages in the sinuses may prolong phage persistence by bypassing the reticuloendothelial system, especially in the presence of remaining bacterial cells, which would enable self-replication. Wright et al[25] reported 200-fold amplification of *P aeruginosa* phages more than 42 days after a single dose of treatment. Multiple studies have also suggested phages may play a protective role and assist in bacterial clearance when subsequent infection is encountered.[31,38,39]

Conclusions

The AB-SA01 phage cocktail for intranasal irrigation appears to be safe and well tolerated to 3×10^9 PFU for 14 days with no dose-limiting adverse effects. The preliminary efficacy data suggest that prolonged antimicrobial effects are possible, allowing for a more targeted approach in treating recalcitrant sinus infections and associated inflammation due to *S aureus*. Further work must be performed to determine the optimal dose regimen and demonstrate the efficacy of AB-SA01 in a statistically powered randomized clinical trial.

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Concept and design: Ooi, Drilling, Morales, Vreugde, Psaltis, Wormald.
Acquisition, analysis, or interpretation of data: Ooi, Morales, Fong, Moraitis, Macias-Valle, Vreugde, Psaltis, Wormald.
Drafting of the manuscript: Ooi, Vreugde.
Critical revision of the manuscript for important intellectual content: Ooi, Drilling, Morales, Fong, Moraitis, Macias-Valle, Vreugde, Wormald.
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Supervision: Drilling, Morales, Macias-Valle, Vreugde, Psaltis, Wormald.

Conflict of Interest Disclosures: Dr Morales reported being employed by AmpliPhi Biosciences Corporation. No other disclosures were reported.

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Additional Contributions: Peter Speck, BSc (Hons), PhD, Biological Sciences, Adelaide, Australia, introduced phage therapy to our department and provided expertise on previous phage studies. Eric Gowans, MAppSc, PhD, Department of Virology and Vaccine Development, Basil Hetzel Institute for Translational Health Research, The University of Adelaide, Adelaide, Australia, participated as our virology expert on our safety monitoring committee. Neither individual received compensation for contributions to this project.

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