

Efficacy and Facial Microbiome Modulation of 30% Supramolecular Salicylic Acid versus Topical Fusidic Acid in Mild-to-Moderate Acne Vulgaris: A Randomized Comparative Study

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Abstract

Background

Acne vulgaris is a common inflammatory dermatosis associated with alterations in the skin microbial ecosystem. Because prolonged topical antibiotic use may contribute to antimicrobial resistance, effective non-antibiotic alternatives are needed.

Objectives

To compare the clinical outcomes and longitudinal skin microbiome changes associated with 30% supramolecular salicylic acid (SSA) peeling and topical fusidic acid (FA) in patients with mild-to-moderate acne.

Methods

This randomized, assessor-blinded, parallel-group trial included 46 participants with evaluable longitudinal clinical and microbiome data (SSA, $n = 23$; FA, $n = 23$). Clinical outcomes were assessed over 8 weeks. Lesional and non-lesional skin samples collected at baseline, Week 4 and Week 8 underwent 16S rRNA gene sequencing. Analyses included baseline-adjusted clinical models, mixed-effects models, within-participant community-distance analyses, restricted-permutation PERMANOVA and ANCOM-BC2 differential-abundance testing with false-discovery-rate correction.

Results

Lesion counts decreased in both groups. At Week 8, the baseline-adjusted total-lesion count ratio for SSA versus FA was 1.01 (95% CI 0.78–1.32), and no clear between-group differences were identified for cumulative 8-week lesion burden or exploratory responder outcomes. For microbiome perturbation relative to each participant's baseline, no treatment-by-time-by-site interaction was detected using Aitchison, Bray–Curtis, weighted UniFrac or unweighted UniFrac distances (all $P \geq 0.468$). No treatment-by-time genus- or ASV-level effect remained significant after Benjamini–Hochberg correction (minimum $q = 0.173$ and 0.248 , respectively).

Conclusions

SSA and FA were associated with similar observed clinical improvement, although this study was not designed to establish equivalence or non-inferiority. Whole-community analyses did not demonstrate detectable differences in microbiome perturbation between treatments or establish a microbiome-sparing advantage for SSA. SSA may represent a clinically reasonable non-antibiotic option, but larger

non-inferiority trials incorporating direct antimicrobial-resistance measurements and longer follow-up are required.

Trial Registration

Chinese Clinical Trial Registry ChiCTR260012977 (Date of registration 20260810), Retrospectively registered.

Introduction

Acne vulgaris (AV) is a prevalent, chronic inflammatory disorder of the pilosebaceous unit, affecting approximately 85% of adolescents and young adults globally¹. It is clinically characterized by comedones, papules, pustules, and in severe cases, nodules and cysts, which can lead to permanent scarring and psychosocial distress². The pathogenesis of acne is multifactorial, encompassing excessive sebum production, follicular hyperkeratinization, colonization by *Cutibacterium acnes*, and dysregulated inflammatory responses. Emerging evidence underscores the pivotal role of cutaneous microbial dysbiosis, which specifically imbalances in the relative abundances of *Cutibacterium acnes*, *Staphylococcus*, and other commensals, plays a critical role in the progression and persistence of disease^{3–5}.

First-line interventions for mild-to-moderate acne typically include topical retinoids, benzoyl peroxide, antibiotics. Among these, fusidic acid is a potent topical antibiotic frequently employed to target bacterial components of acne, but their widespread and prolonged clinical use can led to increasing antimicrobial resistance (AMR) in acne-associated bacteria. Although specific studies on topical fusidic acid resistance in acne are limited, related clinical observations and existing guidelines have warned of the inherent resistance risk of both topical and oral antibiotic, especially with long-term continuous use^{6–8}; Such resistance can impair treatment efficacy, increase disease relapse and disrupt the skin microbiome.

As a non-antibiotic alternative, salicylic acid exhibits keratolytic, anti-inflammatory, and comedolytic activities. Supramolecular salicylic acid (SSA) is its novel formulation, which improves solubility, stability and skin tolerability while retaining SA's therapeutic effects^{2,3,9}; Previous studies have demonstrated that SSA not only reduces sebum production and improves acne lesions but also modulates the cutaneous microbiome by altering the relative abundance of *Cutibacterium acnes*, decreasing the relative abundance of *Staphylococcus* and *Ralstonia*, and mitigating inflammatory markers^{2–4}. Despite the widespread clinical application of fusidic acid and SSA, direct comparative data of their different impacts on facial microbiome composition and diversity remain limited. Given the growing concern over potential antimicrobial resistance and skin microbiome disruption linked to fusidic acid, it is critical to evaluate whether SSA can serve as an effective microbiome-sparing alternative to topical antibiotics. As a result, we conducted a randomized comparative trial to evaluate the clinical efficacy of 30% SSA versus

fusidic acid in patients with mild-to-moderate acne vulgaris. By characterizing differential effects on the facial microbiome, this study aimed to elucidate how these treatments modulate microbial communities and to determine whether such changes correlate with clinical improvement, ultimately informing more effective and well-tolerated strategies for acne management.

Materials and methods

1.Study design

This randomized, assessor-blinded comparative trial lasted 8 weeks. Clinical assessments were performed at baseline and Weeks 2, 4, 6 and 8, and microbiome samples were collected at baseline, Week 4 and Week 8. Participant screening, enrollment, allocation and follow-up should be reported in the CONSORT flow diagram (Fig. 1A, Supplementary Figure S1).

Human Ethics and Consent to Participate declarations

The study was based on the principles of the Declaration of Helsinki and received approval from the institutional review board of Beijing Tongren Hospital, Beijing, China (TREC2024-KY117). All patients provided written informed consent prior to participation.

Clinical trial number

The trial was formally registered with the National Medical Research Registry of China on 2026-08-10 (Registration No. ChiCTR2600129770). Although the registration was performed retrospectively, ethical review approval had been obtained in September 2024 before the commencement of the study. This randomized comparative clinical trial was reported in strict accordance with the Consolidated Standards of Reporting Trials (CONSORT) 2010 statement. A fully completed CONSORT 2010 checklist detailing the location of each reporting item within the manuscript is provided as an additional supplementary file.

2.Patients

Individuals were enrolled in the study from December 2024 to September 2025 at the Department of Dermatology, Beijing Tongren Hospital. Participants aged between 18 and 40 years who fulfilled the China Clinical Dermatology diagnostic criteria for acne vulgaris were included. Exclusion criteria encompassed the presence of concurrent facial skin pathologies, malignancies, or autoimmune disorders, as well as systemic administration of antibiotics and immunosuppressants, chronic anti-inflammatory medications within the preceding four weeks, or the application of any topical therapeutic agents in two weeks.

3.Interventions and parameter assessments

VISIA photographs and facial swabs were collected in all patients at V0 (Baseline), V2 (after 4 weeks) and V4 (after 8 weeks). The evaluation of lesion count was executed by two experienced dermatologists, who appraised the participants' clinical characteristics at each visit, including the aggregate quantities of inflammatory papules, comedos and cysts.

Disease severity was also evaluated by two experienced dermatologists using the IGA (Investigator's Global Assessment) scores based on the features of patients' lesion. Among them, the degree of severity progressively escalates, ranging from 0 to 4. A score of 0 or 1 indicates skin that is either smooth or nearly smooth. A score of 2 denotes a mild condition, which is more severe than a score of 1, characterized by the presence of some non-inflammatory skin lesions and a limited number of inflammatory skin lesions (specifically papules or pustules but not nodular or cystic lesions). A score of 3 signifies a moderate condition, characterized by numerous non-inflammatory skin lesions and a possible occurrence of inflammatory skin lesions, with the number of small nodular or cystic lesions not exceeding one. A score of 4 represents a severe condition, distinguished by the presence of numerous non-inflammatory and inflammatory skin lesions with a minimal number of nodular or cystic lesions.

Participants were randomly allocated by sealed envelopes to 30% supramolecular salicylic acid peeling (SA; Group A) or topical fusidic acid ointment (FA; Group B). SA peeling was administered every 2 weeks for four sessions, whereas FA was self-applied twice daily for 8 weeks. Clinical visits occurred at baseline (V0) and Weeks 2 (V1), 4 (V2), 6 (V3) and 8 (V4).

30% SSA (Broda, Borenda Biochemical Technology, Shanghai, China) was applied to the facial lesions of patients in Group A, in the order of forehead, nose, cheeks, and chin. A layer of sterile water was applied to the patient's face and massaged for a duration ranging from 10 to 15 minutes. Throughout this procedure, sterile water and SSA solution were intermittently added and massaged into the skin to enhance the absorption of the salicylic acid. A total of 2 to 3 layers of SSA was administered in accordance with the patient's dermatological condition. The endpoint response is characterized by the manifestation of consistent erythema or a frosted appearance on the skin lesions of the patients. A cold compress was applied for a duration ranging from 20 to 30 minutes immediately subsequent to the treatment. Patients were instructed to subsequent regimens of moisturization, repairing, and sun protection.

Participants in the FA group were instructed to distribute approximately 1 g of fusidic acid ointment evenly over the facial treatment area twice daily for 8 weeks.

4. Sample collection

Each patient was directed to refrain from washing their face and using any cosmetics for a period of 24 hours preceding the sampling procedure. Facial swabs were collected from lesional and non-lesional sites of patients diagnosed acne vulgaris. Samples were acquired utilizing a sterile cotton swab premoistened with phosphate-buffered saline (PBS), which was then rubbed onto the face ten times. At

the end of the procedure, the distal ends of the swabs were excised from the handles and subsequently introduced into a tube filled with 1.5 mL of PBS. The swab samples were preserved at a temperature of -20°C until the process of DNA extraction was initiated.

5. DNA extraction

All biological specimens were mechanically disrupted using tissue disrupter (TissueLyser; QIAGEN) with 5-mm stainless steel beads (QIAGEN, Hilden, Germany), operating at a frequency of 65 Hz for a duration of 20 minutes. DNA was extracted using the DNeasy Blood and Tissue Kit (QIAGEN) following the manufacturer's instructions. The assessment of the extracted DNA's quality and concentration was conducted using a spectrophotometer (Nanodrop 2000, manufactured by ThermoFisher Scientific in Waltham, MA, USA) and then store the DNA at -80°C before undergoing PCR analysis.

6. Gene amplification, library preparation and sequencing

DNA was specifically targeted using primers designed for V3-V4 region of the bacterial 16S rRNA gene. A commercially available kit, the TruSeq DNA PCR-Free Sample Preparation Kit from Illumina Inc., based in San Diego, CA, USA, was utilized to prepare the amplicon library. Subsequently, the library was quantified through fluorometry (Qubit; ThermoFisher Scientific) and quantitative PCR analyses. The samples were sequenced (HiSeq 2500 platform; Illumina) by an external company, Novogene Bioinformatics Technology Co. Ltd, located in Beijing, China.

7. Data analysis

Analyses were performed in R version 4.5.2. Continuous and categorical variables were summarized using standard descriptive statistics. Clinical trajectories were visualized using participant-level profiles and group means with 95% confidence intervals (CIs). Total, inflammatory and comedonal lesion counts at Weeks 4 and 8 were analyzed using negative-binomial regression adjusted for baseline values, with effects reported as SA/FA count ratios. Disease-burden area under the curve (Weeks 0–8) was calculated using the trapezoidal rule and compared using baseline-adjusted linear regression with HC3 robust CIs.

Alpha diversity was assessed using Shannon and Simpson indices. Beta diversity was evaluated using Aitchison, Bray–Curtis, and weighted and unweighted UniFrac distances. Microbiome perturbation was defined as the distance from each Week-4 or Week-8 sample to the corresponding participant- and site-specific baseline. Perturbation and lesional–non-lesional (LS–NLS) distances were analyzed using mixed-effects models with treatment, visit, skin site and their interactions as fixed effects and participant as a random intercept. The 10 most abundant genera and exploratory compositional indices were analyzed descriptively or using participant-random-intercept mixed models. Log-ratios used a 0.5-count pseudocount. Differential abundance was assessed using ANCOM-BC2 after 20% prevalence

filtering, including treatment-by-visit effects, skin site and a participant random intercept; MaAsLin2 was used for sensitivity analysis. Clinical–microbiome associations and baseline predictors were exploratory, with prediction models evaluated using 1,000 participant-level bootstrap resamples. Statistical significance was defined as two-sided $P < 0.05$ for primary model terms and FDR-adjusted $q < 0.05$ for differential-abundance analyses.

Results

1. Patient demographics

A total of 46 randomized participants (SA, $n = 23$; FA, $n = 23$) had complete longitudinal clinical data and qualified microbiome samples for further analysis. Baseline clinical and demographic characteristics were broadly comparable between groups (Table 1).

Table 1
Baseline demographic and clinical characteristics of the clinical analysis population.

	SA ($n = 23$)	FA ($n = 23$)	<i>P</i> value
Number (<i>n</i>)	23	23	/
Gender (Female:Male)	15:8	19:4	0.19
Age (Mean $\pm$ SD, yr)	23.57 $\pm$ 3.70	24.17 $\pm$ 4.09	0.60
IGA score (Mean $\pm$ SD)	3.09 $\pm$ 0.29	2.92 $\pm$ 0.41	0.10
Lesion count (Mean $\pm$ SD)	41.26 $\pm$ 22.85	32.21 $\pm$ 15.26	0.12
Inflammatory papule	19.13 $\pm$ 8.28	15.33 $\pm$ 6.47	0.09
Comedo	22.00 $\pm$ 22.31	16.79 $\pm$ 17.21	0.38
Cyst			/
SD= standard deviation; IGA score= Investigator’s Global Assessment ; Lesion count = Sum numbers of Inflammatory papules + Comedones + Cysts			

2. Clinical parameters and efficacy

Total, inflammatory and comedonal lesion counts decreased over 8 weeks in both groups (Fig. 1B, Table 2). In baseline-adjusted negative-binomial models, the SA/FA lesion-count ratios were 1.05 (95% CI 0.89–1.24) at Week 4 and 1.01 (0.78–1.32) at Week 8 for total lesions; 1.12 (0.89–1.42) and 1.02 (0.74–1.39) for inflammatory lesions; and 0.95 (0.74–1.21) and 1.00 (0.75–1.35) for comedones, respectively (Fig. 1C). Thus, no clinically or statistically clear between-group difference was identified at either time point.

Table 2
Descriptive total lesion counts and IGA scores at baseline and Week 8

		BT(V0)	AT(V4)	t-Value	P-Value
Lesion count	SA	41.26 ± 22.85	24.96 ± 10.10	3.39	0.003
	FA	32.21 ± 15.26	22.88 ± 12.41	2.89	0.008
IGA score	SA	3.09 ± 0.29	2.70 ± 0.56	3.76	0.001
	FA	2.92 ± 0.41	2.42 ± 0.58	4.15	< 0.001
BT: Before treatment; AT: After treatment.					

Cumulative 0-8-week disease burden was also similar. Baseline-adjusted SA-minus-FA AUC differences were 4.13 lesion-count weeks (95% CI -21.99 to 30.25) for total lesions, 1.94 (-19.19 to 23.08) for inflammatory lesions and - 7.31 (-24.94 to 10.31) for comedones (Supplementary Figure S2). At Week 8, at least 30% total-lesion reduction occurred in 52.2% of SA and 58.3% of FA participants, at least 50% inflammatory-lesion reduction in 21.7% and 37.5%, and an IGA decrease of at least one grade in 39.1% and 54.2%, respectively (Fig. 1D).

It is of particular note that our study encompassed 4 individuals presenting with mild facial cystic acne at baseline (Sum number of cysts ≤ 2). These patients were evenly distributed, with two allocated to Group A and two to Group B. Following a four-week therapeutic regimen, it was observed that the cysts in two patients from Group A and one from Group B experienced regression, with no subsequent recurrence noted. Nevertheless, an additional patient from Group B experienced a relapse two weeks subsequent to the initial amelioration of the cyst.

3. Observation of Adverse Reactions

A total of 7 patients (30.4%) in Group A experienced symptoms such as dry skin desquamation or mild redness after treatment. All symptoms were relieved within one week after moisturizing and sun protection. It is worth noting that one patient in Group A experienced a recurrence of herpes simplex after the fourth treatment, presenting with clustered blisters around the mouth accompanied by pain. Her last recurrence occurred two years ago, suggesting that salicylic acid may have a stimulating effect. This is consistent with the current research results¹⁰. In a comprehensive chemical peels guideline, "HSV recurrence" is clearly listed as one of the main risks and the specific usage methods of antiviral drugs are necessary¹¹.

4. Alpha diversity and whole-community structure

Within-participant Shannon diversity showed substantial overlap between LS and NLS samples at baseline, Week 4 and Week 8, without a consistent treatment-specific separation (Fig. 2A). Weighted-

UniFrac PCoA likewise showed overlapping FA and SA distributions and heterogeneous participant-level trajectories at both skin sites (Fig. 2B). Restricted longitudinal PERMANOVA did not identify a treatment-by-time-by-site effect for Aitchison ($p = 1.000$), Bray-Curtis ($p = 0.995$), weighted UniFrac ($p = 0.832$) or unweighted UniFrac distance ($p = 0.913$). PERMDISP indicated unequal Aitchison dispersion at Week 4 NLS ($p = 0.032$), warranting caution for that stratum.

Participant-specific perturbation from baseline was heterogeneous. Mixed models did not detect a treatment-by-time-by-site interaction for Aitchison ($p = 0.957$), Bray-Curtis ($p = 0.934$), weighted UniFrac ($p = 0.553$) or unweighted UniFrac distance ($p = 0.468$) (Fig. 3A). LS-NLS distances generally did not differ in longitudinal change between treatments; the Week-8 interaction for unweighted UniFrac was nominally significant (estimate -0.057 , $p = 0.013$) but arose among multiple exploratory distance tests. LS distance to the external healthy genus centroid decreased over time in FA, but treatment-by-time contrasts were not significant at Week 4 ($p = 0.084$) or Week 8 ($p = 0.313$) (Fig. 3B).

5. Taxonomic composition and differential abundance

Cutibacterium, *Staphylococcus* and *Corynebacterium* were the dominant genera across treatment groups, visits and skin sites (Fig. 4A). The baseline relative abundance and changes of these major bacterial taxa are detailed in Supplementary Tables 1 and 2. Exploratory compositional-index models suggested a larger Week-4 decrease in Pielou evenness (treatment-by-visit estimate -0.118 , $p = 0.004$) and increase in genus dominance (estimate 0.199 , $p = 0.006$) in SA relative to FA at lesional skin, but these nominal p values were not adjusted across the several exploratory indices (Supplementary Figure S3).

After 20% prevalence filtering, ANCOM-BC2 evaluated 176 genera and 151 ASVs. No treatment-by-time effect passed BH-FDR correction at either taxonomic level (minimum interaction $q = 0.173$ for genera and $q = 0.248$ for ASVs) (Fig. 4B). *Corynebacterium* at Week 4 had the smallest genus-level interaction q value but was not statistically significant after multiplicity correction. MaAsLin2 sensitivity results were directionally compared with ANCOM-BC2 (Supplementary Figure S5).

6. Clinical-microbiome integration

Changes in inflammatory lesion counts were only weakly related to changes in lesional Shannon diversity (Spearman ρ from -0.27 to 0.09 across treatment and follow-up strata) (Fig. 5A). The benefit-disturbance analysis showed wide participant-level heterogeneity without a clear separation of SA and FA into distinct clinical-benefit/ecological-cost regions (Fig. 5B). In separate bootstrap models, baseline Shannon LS-NLS difference, LS-NLS Aitchison distance and the *Cutibacterium*/*Staphylococcus* ratio did not show stable treatment-effect modification. Distance to the healthy genus centroid yielded a bootstrap interaction CI narrowly above zero, but this was one of four exploratory predictors in only 46 participants and was considered hypothesis-generating (Supplementary Figure S4).

Discussion

In this randomized, assessor-blinded trial, three principal findings emerged. First, both SSA and FA were associated with reductions in total, inflammatory and comedonal lesion counts over 8 weeks, and the baseline-adjusted between-group estimates did not show a clear difference. This pattern was consistent across baseline-adjusted lesion counts, cumulative 0–8-week disease burden and exploratory responder outcomes. However, the confidence intervals remained sufficiently wide that equivalence or non-inferiority cannot be concluded. Second, longitudinal whole-community analyses did not identify differential microbiome displacement between the two treatments across lesional and non-lesional sites. Third, no genus-or ASV-level treatment-by-time effect survived false-discovery-rate correction. Collectively, these findings suggest that SSA achieved similar observed short-term clinical improvement without evidence of greater microbial community perturbation than FA.

The observed clinical improvement with SSA is consistent with previous studies reporting reductions in acne lesions and sebum production following treatment with 30% or lower-concentration supramolecular salicylic acid formulations.^{2–4} The effects of SSA may reflect its keratolytic and comedolytic activity within the pilosebaceous unit, together with anti-inflammatory and sebum-regulating actions. Salicylic acid has also been reported to influence sebocyte lipogenesis through the AMPK/SREBP1 pathway.^{12,13} Nevertheless, these mechanisms were not directly measured in the present study, and the current results should therefore be interpreted as clinical and ecological observations rather than mechanistic evidence. The similar observed improvement with SSA and FA supports further evaluation of SSA as a non-antibiotic treatment option, but does not establish clinical non-inferiority or a reduction in antimicrobial-resistance risk.

A distinctive feature of this study was the evaluation of ecological displacement relative to each participant's own baseline. This within-participant approach reduces the influence of the substantial interpersonal variation characteristic of the skin microbiome and more directly quantifies treatment-associated community change. Across Aitchison, Bray-Curtis, weighted UniFrac and unweighted UniFrac distances, no treatment-by-time-by-site interaction was detected. Thus, the data did not show that SSA produced greater community displacement than FA.

Analyses of movement toward the non-lesional or healthy-control microbial reference provided complementary but exploratory information. Healthy controls were not randomized and raw healthy-control count data were unavailable for all analyses; therefore, the healthy centroid should be regarded as an external ecological reference rather than a causal treatment target. The nominal Week 4 differences in Pielou evenness and community dominance also did not survive multiplicity correction. These findings illustrate that higher diversity or evenness should not automatically be equated with a healthier skin microbiome, particularly in an ecosystem normally dominated by a limited number of commensal taxa.^{5,9,14}

Neither the genus-level nor ASV-level ANCOM-BC2 analysis identified a treatment-by-time signal after false-discovery-rate correction, and the sensitivity analyses did not provide robust evidence of treatment-specific taxonomic changes. Nominal changes involving *Staphylococcus* should therefore be viewed as hypothesis-generating. Moreover, relative-abundance changes cannot establish antibiotic selection pressure or antimicrobial resistance. Such conclusions would require resistance-gene profiling, culture-based susceptibility testing or strain-resolved metagenomic analysis.^{7,8,15} Similarly, genus-level detection of *Cutibacterium* cannot distinguish acne-associated and health-associated *C. acnes* lineages.^{5,16–18}

Associations between changes in inflammatory lesion counts and changes in Shannon diversity or selected microbial indices were weak and exploratory. The benefit-disturbance analysis likewise did not reveal a clear separation between treatments. These observations suggest that short-term clinical improvement may not be mediated by broad changes in community diversity detectable by 16S sequencing. The therapeutic effects of SSA may instead involve keratolytic, comedolytic or anti-inflammatory pathways, or microbial changes occurring at the strain or functional level; however, these mechanisms were not directly evaluated in the present study.^{12,13}

Local reactions reported in the SSA group were generally mild and transient: seven participants experienced dryness, desquamation or mild erythema, and these symptoms resolved within one week with moisturization and photoprotection. One participant with a previous history of herpes simplex experienced recurrence after the fourth peeling session. HSV reactivation is a recognized potential complication of facial chemical peeling, suggesting that a history of recurrent herpes should be assessed before treatment and that antiviral prophylaxis may be considered according to individual risk.^{10,11} Because adverse events were uncommon and the sample was small, no comparative conclusion regarding the tolerability of SSA and FA should be drawn.

This study has several limitations. First, microbiome analyses relied on surface-swab 16S rRNA sequencing and relative-abundance data, which cannot quantify absolute bacterial load, reliably resolve strain-level variation or directly assess antimicrobial resistance. Second, the healthy controls constituted an external reference rather than a randomized comparison group, and complete raw count data were not available for all healthy-centroid analyses. Third, treatment route and schedule differed between groups, participant blinding was not feasible, and adherence and concomitant skincare practices may have introduced additional variability. Finally, the 8-week follow-up did not permit evaluation of recurrence, longer-term ecological recovery or the emergence of antimicrobial resistance. Future studies should use an adequately powered non-inferiority design, prespecify a limited number of ecological endpoints and extend follow-up beyond treatment cessation. Incorporating absolute bacterial quantification, shotgun metagenomics, strain-resolved *C. acnes* analysis, resistance-gene profiling and phenotypic antimicrobial susceptibility testing would allow the clinical efficacy, ecological consequences and antimicrobial-stewardship value of SSA to be assessed more definitively.

Conclusions

In patients with mild-to-moderate acne, SSA and topical FA were associated with similar observed clinical improvement over 8 weeks. No detectable difference in whole-community microbiome perturbation was identified, and treatment-specific taxonomic findings did not remain significant after false-discovery-rate correction. These results support further evaluation of SSA as a non-antibiotic treatment strategy but do not establish clinical non-inferiority, microbiome superiority or a reduction in antimicrobial-resistance risk.

Abbreviations

AV

Acne vulgaris

SSA

Supramolecular salicylic acid

FA

Fusidic acid

IGA

Investigator's Global Assessment

AMPK

AMP-activated protein kinase

SREBP-1

Sterol regulatory element-binding transcription factor 1

NF- κ B

Nuclear factor kappa B

PBS

Phosphate-buffered saline

PCR

Polymerase chain reaction

PCoA

Principal coordinate analysis

NMDS

Non-metric Multidimensional Scaling

HC

Healthy controls

SD

Standard deviation

IQR

Interquartile range

MR

Medical Research Registry

HSV
Herpes simplex virus
ASV
Amplicon sequence variant
AUC
Area under the curve
CLR
Centered log-ratio
FDR
False discovery rate
PERMANOVA
Permutational multivariate analysis of variance
PERMDISP
Permutational analysis of multivariate dispersions
ANCOM-BC2
Analysis of compositions of microbiomes with bias correction 2

Declarations

Ethics approval and consent to participate

This trial complied with the Declaration of Helsinki, approved by the Institutional Review Board of Beijing Tongren Hospital (TREC2024-KY117) and registered in the National Medical Research Registry of China (ChiCTR2600129770). All participants provided written informed consent before enrollment, sampling and treatment.

Availability of data and materials

Raw 16S rRNA sequencing data generated in this study were deposited in the NCBI Sequence Read Archive (SRA) database under BioProject accession number PRJNA1497343. The datasets generated and analysed during the current study are available in the NCBI repository, <https://www.ncbi.nlm.nih.gov/sra/PRJNA1497343>

Consent for publication

Not Applicable.

Competing Interests

The authors declare that there are no financial or non-financial competing interests relevant to this research.

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Authors' contributions

Rong Tao: Conceptualization, Methodology, Investigation, Resources, Data curation, Formal analysis, Funding acquisition, Supervision, Writing – review & editing. Jinghan Yuan: Data curation, Formal analysis, Clinical investigation, Writing – original draft.

Yutong Xie: Patient recruitment, Data curation, Methodology support, Writing – original draft.

Can Cui: Clinical sample collection, Data curation, Case follow-up, Methodology assistance.

Ruojun Wang: Clinical data sorting, Supplementary data collation.

Aihua Wei: Funding acquisition, Project supervision, Critical revision of the manuscript.

All authors read the final version of the manuscript and provided full approval for submission.

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Figures

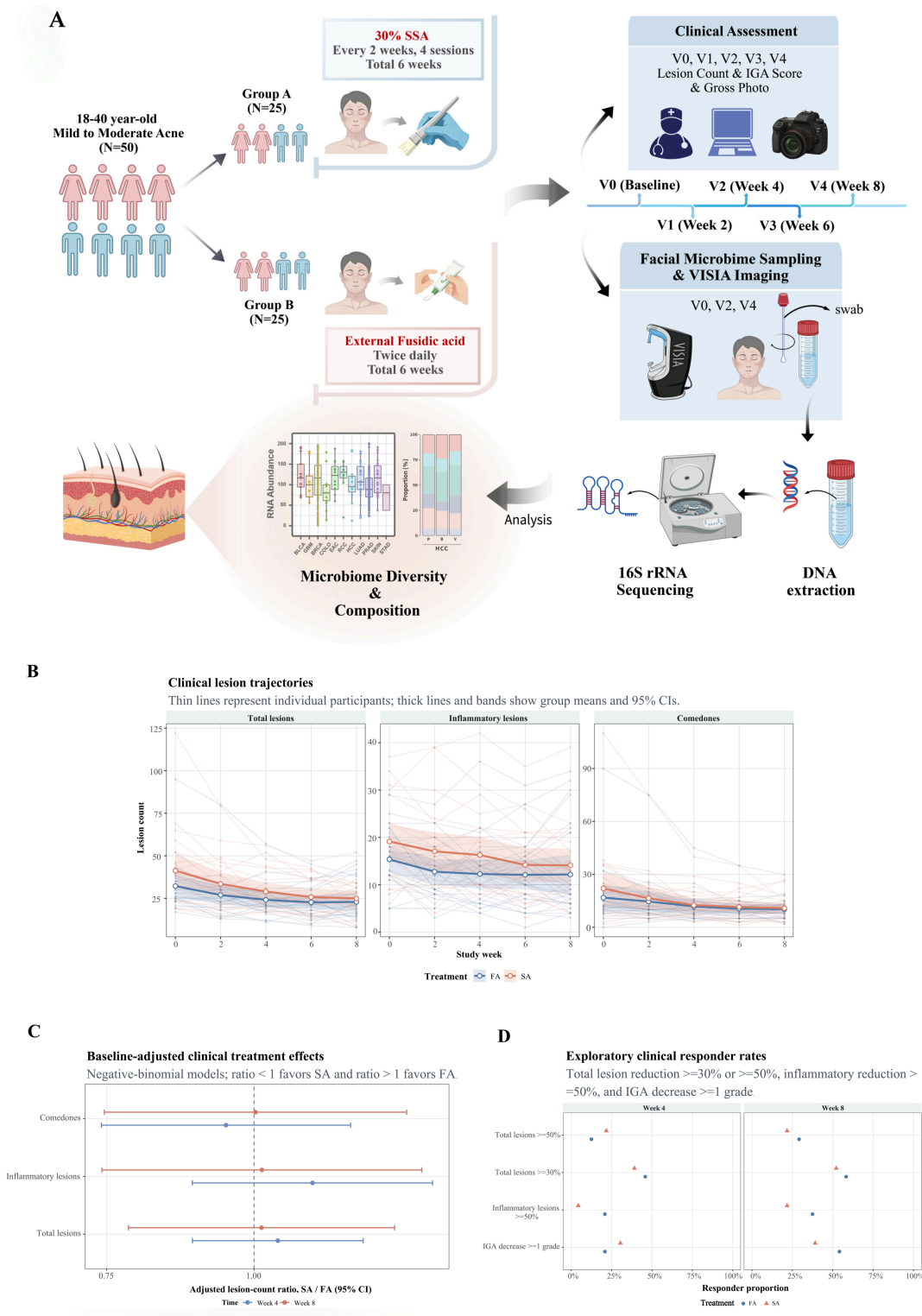
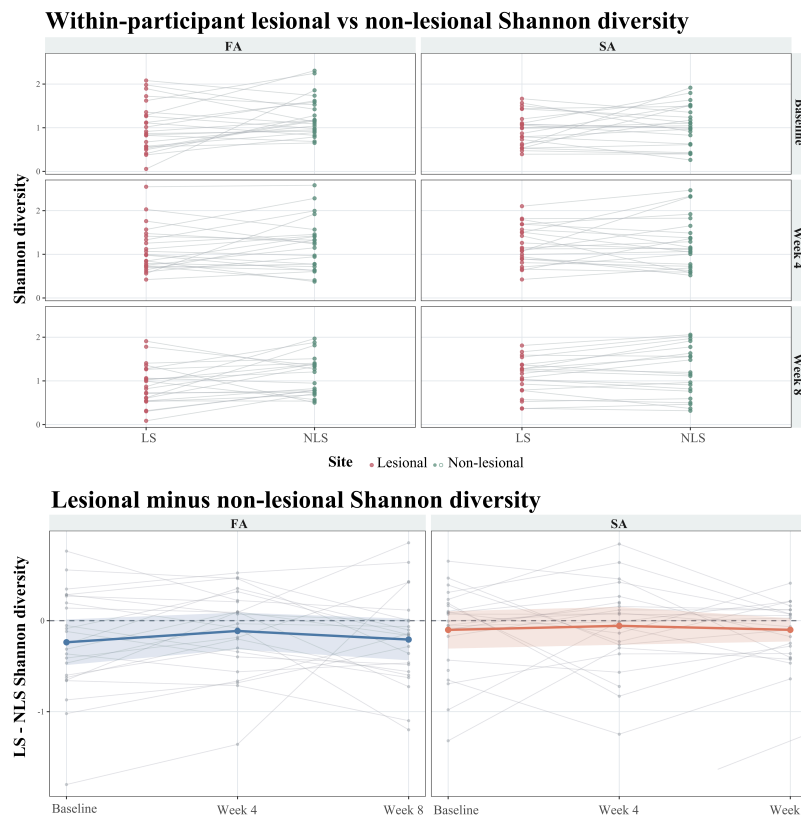


Figure 1

Longitudinal clinical efficacy of supramolecular salicylic acid (SA) and fusidic acid (FA). (A) Schematic flowchart of the overall technical roadmap of this study. (B) Individual trajectories and group means with 95% CIs for total lesions, inflammatory lesions and comedones. (C) Baseline-adjusted negative-binomial lesion-count ratios (SA/FA) at Weeks 4 and 8; ratios below 1 favor SA and ratios above 1 favor FA. (D) Exploratory responder proportions at Weeks 4 and 8. Responder thresholds were not prespecified.

A



B

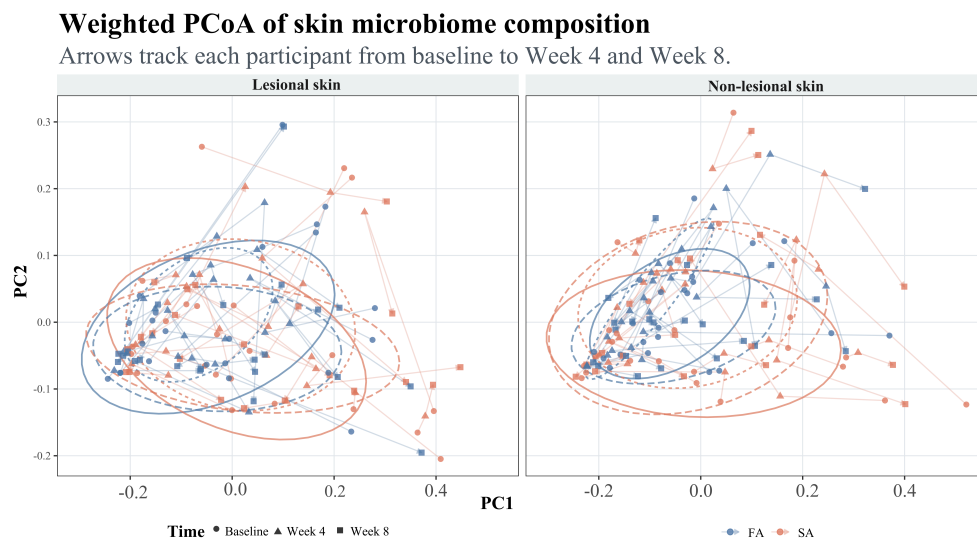


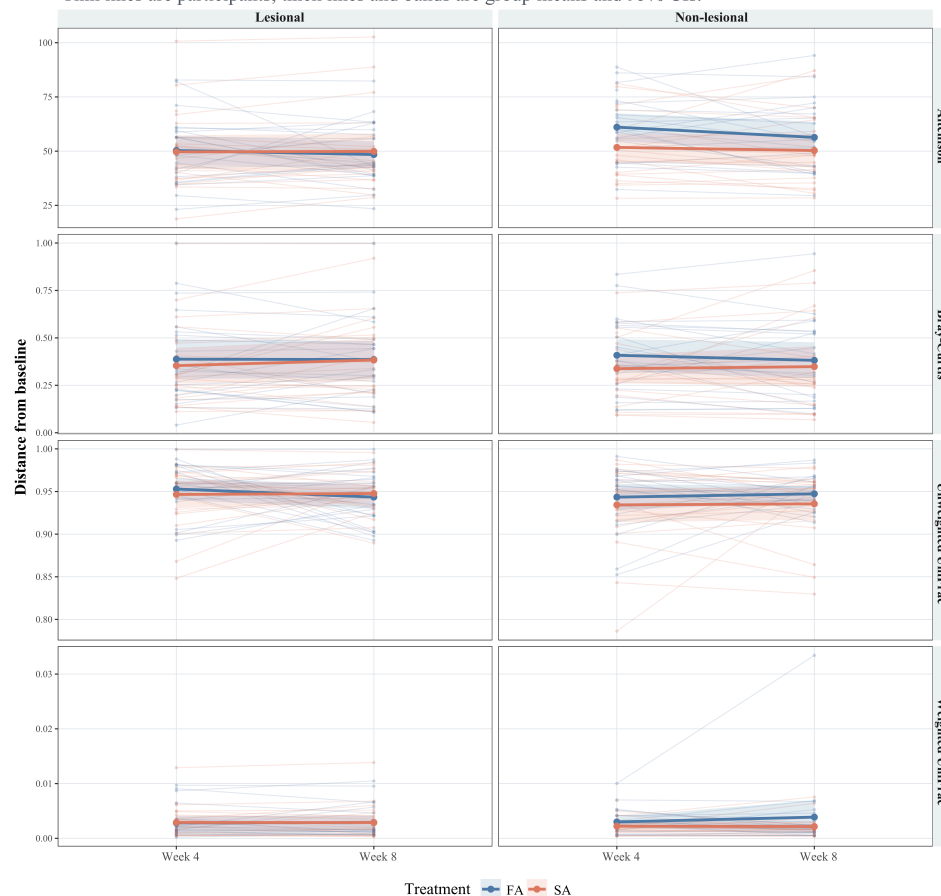
Figure 2

Alpha diversity and whole-community structure. (A) Paired lesional (LS) and non-lesional (NLS) Shannon diversity and the within-participant LS-NLS difference at baseline, Week 4 and Week 8. (B) Weighted-UniFrac PCoA by treatment and skin site; arrows connect each participant's serial samples. PCoA is descriptive, and ellipses do not represent hypothesis tests.

A

Individual microbiome perturbation from each participant's baseline

Thin lines are participants; thick lines and bands are group means and 95% CIs.



B

Microbiome recovery toward non-lesional and healthy reference states

Lower values indicate greater similarity. Healthy controls are an external genus-level ecological reference.

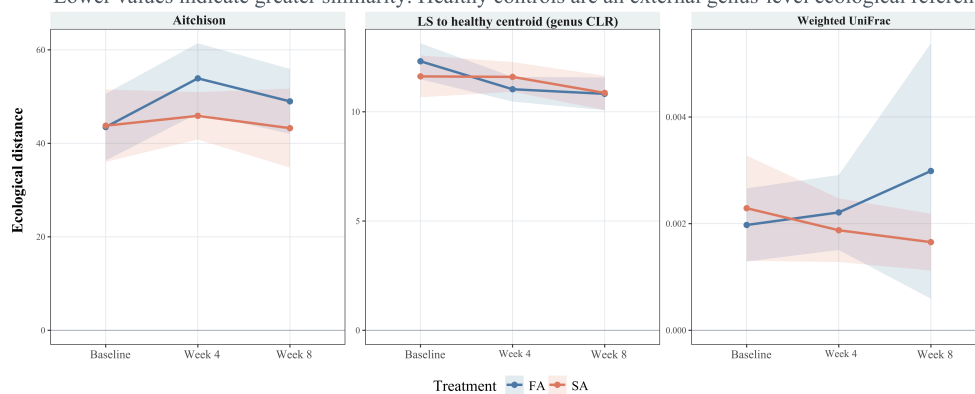
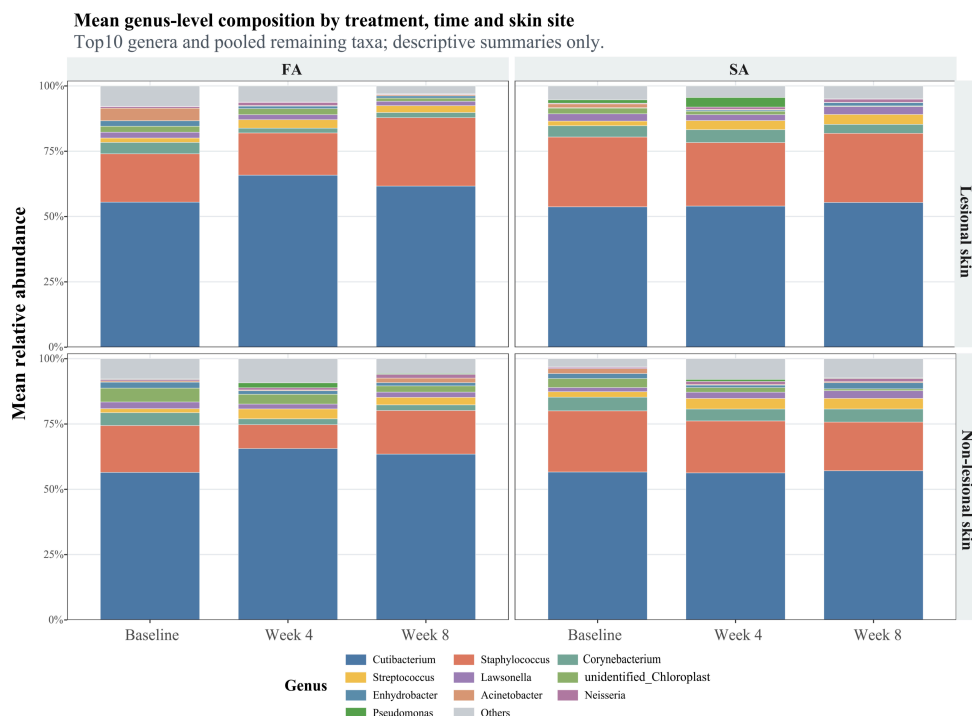


Figure 3

Genus-level composition and longitudinal differential abundance. (A) Mean Top-10 genus composition by treatment, visit and skin site; this panel is descriptive. (B) ANCOM-BC2 treatment-by-time effects after 20% prevalence filtering, adjusted for site and repeated measurements. Positive values indicate a larger change in SA than FA. No displayed effect passed BH-FDR $q < 0.05$.

A



B

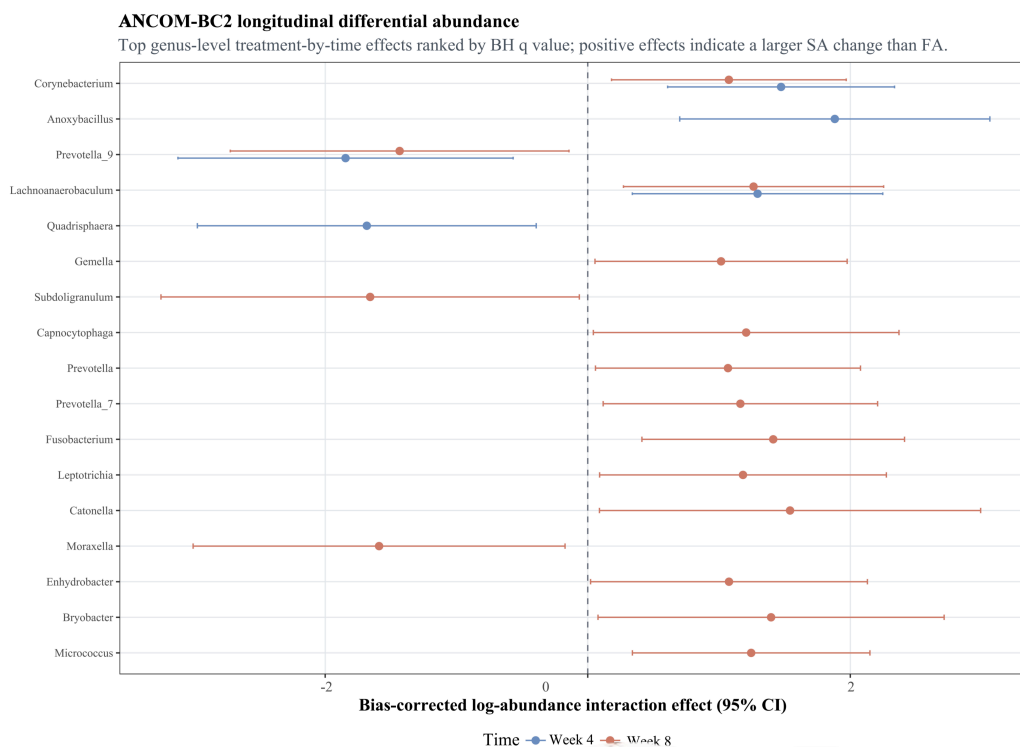


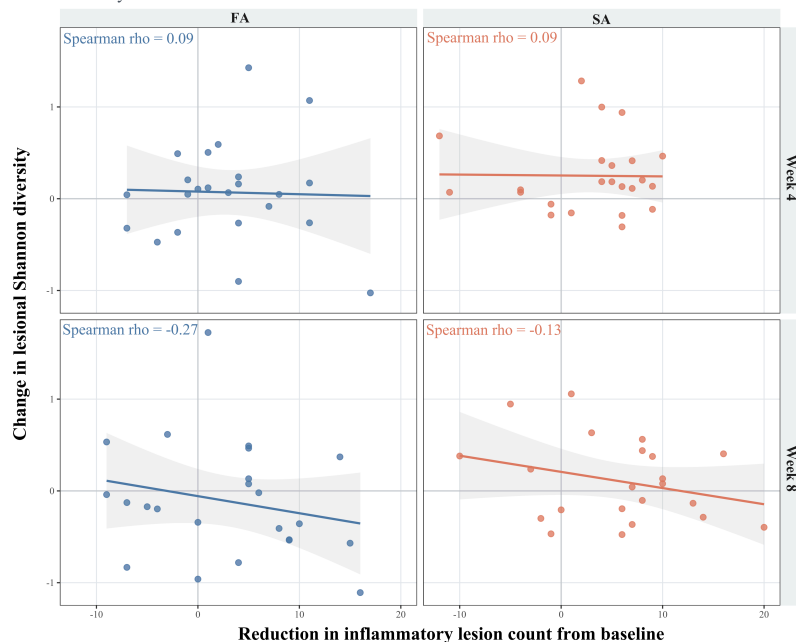
Figure 4

Individual ecological perturbation and recovery. (A) Aitchison, Bray-Curtis, unweighted-UniFrac and weighted-UniFrac distances from each participant's site-specific baseline at Weeks 4 and 8. (B) LS-NLS Aitchison and weighted-UniFrac distances and LS distance to the healthy genus-level CLR centroid. Lower values indicate greater similarity. Healthy controls are an external ecological reference, not a randomized comparator.

A

Association between clinical improvement and lesional Shannon diversity change

Positive lesion reduction denotes improvement; positive Shannon change denotes increased alpha diversity.



B

Clinical benefit versus microbiome perturbation

Upper-right: larger improvement but larger disturbance; lower-right: larger improvement with smaller disturbance.

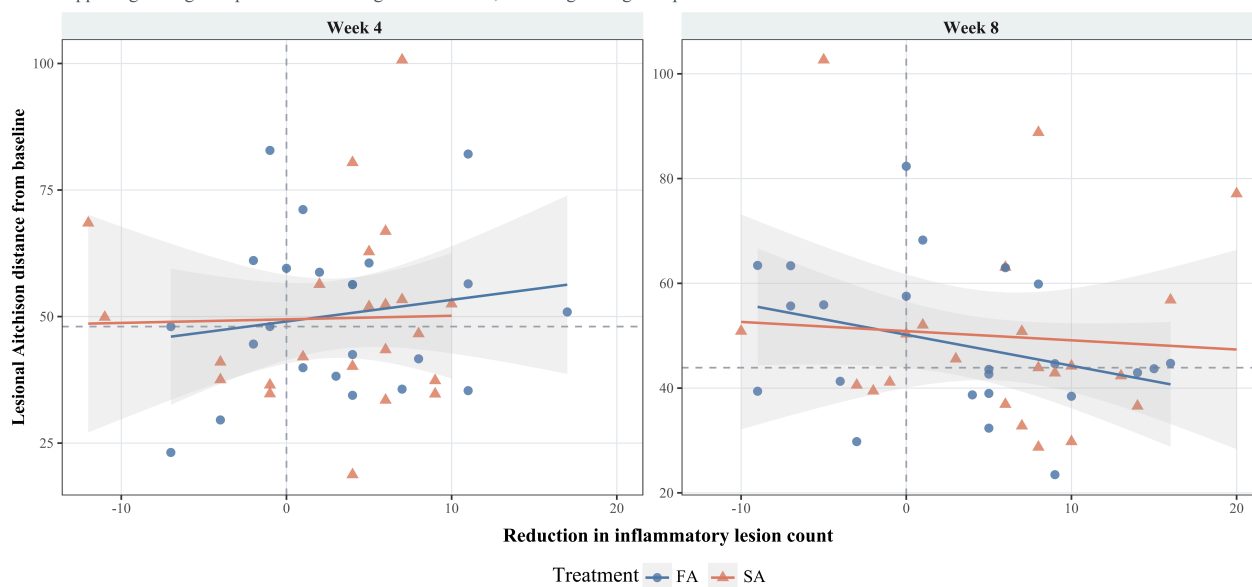


Figure 5

Clinical-microbiome integration. (A) Exploratory associations between reduction in inflammatory lesion count and change in lesional Shannon diversity at Weeks 4 and 8. (B) Individual clinical benefit versus lesional Aitchison perturbation from baseline. The lower-right region represents greater clinical improvement with smaller ecological displacement. Associations are descriptive and do not imply mediation or causality.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [SupplementaryFigureS1.png](#)
- [SupplementaryFigureS4baselinepredictors.png](#)
- [SupplementaryFigureS2clinicalAUC.png](#)
- [SupplementaryFigureS5DAsensitivity.png](#)
- [SupplementaryFigureS3exploratorytaxaindices.png](#)
- [SupplementaryMaterial.docx](#)