Review Article

The Effect of Biologics on the Cutaneous Microbiome in Atopic Dermatitis: A Review

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Atopic dermatitis (AD) is a chronic, inflammatory skin disease characterized by dry patches, itch, and rash that create a burden for patients. A driving factor behind AD pathogenesis and disease severity is dysbiosis. This narrative review explores the effect of different biologic therapies on shifting the microbiome composition to a less inflammatory state and its impact on AD.

INTRODUCTION

Atopic dermatitis (AD) is a chronic, relapsing, inflammatory skin disease characterized by eczematous patches and persistent itch that impacts both adults and children and varies greatly between individuals.[1,2] Disease progression is dependent upon the interaction between skin barrier dysfunction, inflammation, skin microbiome, and itch.[1,3] In both adults and children, AD negatively impacts quality of life.[4] Safe, effective treatments that manage AD long-term are a necessity.

The underlying pathophysiology of AD is not completely understood. One main area of interest is the role of the skin microbiome bacterial abundance and diversity in AD pathogenesis.[5,6] Patients with AD have an increased abundance of *Staphylococcus aureus* bacteria in their skin microbiome compared to patients without the condition, with studies documenting *S. aureus* in 79% of AD skin samples.[5,6] Additionally, there is a significant difference in *S. aureus* abundance between lesional and non-lesional skin, with *S. aureus* detected in 49% of lesional samples and 28% of non-lesional samples ($p<0.001$).[6] Different AD treatments have demonstrated the ability to shift the microbiome towards a healthy state (increased bacterial diversity and reduced *S. aureus* colonization) and improve AD symptoms.[5] *S. aureus* has also been demonstrated to be directly involved in the activation of Th2 lymphocytes and release of inflammatory type 2 cytokines (such as IL-4 and IL-13), further increasing inflammation and AD symptoms.[7-9]

S. aureus releases several toxins and virulence factors that contribute to atopic dermatitis by disrupting the skin barrier and promoting inflammation.[10] For example, V8 serine protease has been implicated in epidermal barrier dysfunction in mice, enterotoxins and TSST-1 cause excessive T cell cytokine production, and beta-toxin causes mast cell degranulation and allergic skin inflammation.[11]

High proportions of *Staphylococcus* and low microbial diversity are associated with AD flares.[12] There are several methods to assess microbiome diversity, including the alpha, beta, or Shannon diversity indices. Alpha diversity is a measure of total species diversity within a community, such as an individual's cutaneous microbiome.[13] Beta diversity compares species diversity between communities.[14] Finally, the Shannon index is a measure of alpha diversity that includes data about species richness (total number) and evenness (how many individuals per species).[15] Significant associations have been found between high *Staphylococcus* density on both lesional and non-lesional skin and AD severity over time. Similarly, significantly higher *Staphylococcus* density was noted on lesional skin compared to non-lesional skin, compared to control skin.[16] Commensal skin bacteria maintain skin barrier homeostasis by inhibiting *S. aureus* and other pathogenic bacteria virulence factors to decrease skin barrier damage and *S. aureus*-associated inflammation, and several systemic therapies have demonstrated the ability to increase commensal bacterial diversity.[10]

Effective therapy seems to improve microbiome diversity and decrease *S. aureus* abundance, even via therapies that are not directly antimicrobial. In rats, systemic corticosteroid treatment was correlated with increased gut fungal microbiome diversity, which could influence fecal metabolite production and the host immune system.[17] The topical corticosteroid fluticasone has never been characterized as directly antibacterial, however, it has been demonstrated to impact the skin microbiome by decreasing *S. aureus* abundance on lesional skin and restoring bacterial diversity to that of control skin samples.[18] Other therapies, such as biologics, inhibit inflammatory cytokines, including dupilumab (IL-4, IL-13),[11-13,19-23] and tralokinumab (IL-13),[10] and are associated with decreased *S. aureus* abundance and increased microbial diversity in patients with AD. This review explores the impact of biologics on the microbiome in atopic dermatitis patients.

CHANGE IN SKIN BACTERIAL MICROBIOME

Hartman et al compared dupilumab treatment to both cyclosporine and healthy volunteer controls with no history of AD or other allergic diseases/chronic inflammation. (See Table 1) The study found that at baseline, the skin microbiome of AD patients was characterized by more *S. au-*

reus bacteria (98% in lesional samples, 87% in non-lesional samples) than healthy controls (28%), and a significantly lower alpha diversity and bacterial community structure between the two groups ($P < 0.001$).[19] Post-dupilumab treatment, the beta bacterial diversity structure of patients shifted closer to that of the healthy controls.[19] Dupilumab treatment resulted in a decrease in *S. aureus* colonization and an increase in microbial diversity and abundance of *S. hominis* in both treatment responders and non-responders, indicating that the change in skin microbiome is partially independent of any clinical response.[19] Responders to dupilumab had a greater significant decrease in *S. aureus* and increase in *S. hominis* compared to cyclosporine responders.[19] Remarkably, after 3 months of treatment, no significant change in bacterial abundance or diversity was evidenced in both responders and non-responders to cyclosporine.[19] Limitations of this study were its non-randomized methods and small sample size.[19] Strengths included the use of a positive and negative control (cyclosporine treatment and healthy controls, respectively).[19]

Olesen et al. investigated the change in the skin microbiome post-dupilumab treatment compared to non-targeted therapies (topical corticosteroids (n = 13), topical calcineurin inhibitors (n = 1), methotrexate (n = 2), and azathioprine (n = 1)) and healthy controls.[20] At baseline, the proportion of *S. aureus* colonization on non-lesional skin positively correlated with baseline EASI score. At the end of treatment, patients who received dupilumab had an average 70.0% reduction in EASI score ($P < 0.001$) compared to the average 24.4% reduction in the non-targeted treatment group ($P < 0.001$).[20] Post dupilumab therapy, the Shannon diversity index significantly increased on lesional skin ($P = 0.005$) and bacterial community structure changed on both lesional and non-lesional skin ($P < 0.001$). Changes included a decrease of *S. aureus* on both lesional ($P = 0.001$) and non-lesional skin ($P < 0.001$) and an increase in *S. hominis* and *S. epidermidis* on non-lesional skin ($P < 0.001$).[20] After dupilumab treatment, there was a significant difference in *S. aureus* reduction on lesional and non-lesional skin ($P < 0.001$).[20] No such change was found in the non-targeted therapy group.

Notably, EASI score improvement was correlated with an increase in Shannon diversity index post-dupilumab, increase in *S. hominis* and *S. epidermidis* abundance ($P = 0.003$, $P = 0.003$, respectively), and decrease in *S. aureus* abundance ($P = 0.001$).[20] Furthermore, *S. aureus* and *S. hominis*/*epidermidis* relative abundances were inversely correlated on both lesional and non-lesional skin.[20] Limitations include the lack of a healthy control group and the non-randomized nature of the study.[20] Strengths of the study include using both 16S rRNA and *tuf* amplification to provide more detail about the abundance of each *Staphylococcus* species present in the skin microbiome.[20]

Simpson et al demonstrated significant reductions in *S. aureus* colonization after 3 days of dupilumab treatment, which thus far is the fastest reduction evidenced in the literature.[21] A greater reduction in SCORAD scores was evidenced by day 14 in dupilumab versus placebo groups ($P = 0.04$) and a greater reduction in EASI, IGA, and NRS scores was measured by day 21.[21] Placebo group clinical improvement from baseline only occurred when switched to dupilumab during the 10 week open label period by 5 weeks into the OLE ($P < 0.001$).[21] Similarly, *S. aureus* cytotoxins were significantly reduced in the dupilumab group lesional skin by day 3.[21] Shannon microbial diversity index increased in dupilumab-treated lesional skin by day 3, and the placebo group showed no change in *S. aureus* reduction or increase in Shannon microbial diversity index until entering the OLE period.[21] Limitations of this study include small sample size. Strengths of this study include the use of 8 different academic centers, randomization, a placebo control, and including measures of inflammation (CCL17 concentration).[21]

Umemoto et al explored the relationship between dupilumab treatment and bacterial skin microbiomes. At baseline, 44.3% of lesional skin bacteria were of the *Staphylococcus* genus, which decreased to 11.8% post 12-weeks of dupilumab treatment.[22] Shannon microbial diversity index increased by week 2 of treatment ($P < 0.01$), and by week 12 was similar to that of healthy controls.[22] A strong correlation was found between *S. aureus* colonization and EASI score at all sampling points during the study (0.51-0.90).[22] Limitations of the study include the small sample size and the lack of randomization. Strengths of the study include the use of a healthy control.[22]

Beck et al conducted a long-term study to investigate the impact of the IL-13 monoclonal antibody tralokinumab on skin microbiota. At baseline, moderate correlations between *S. aureus* and IL-13, IL-22, CCL17, and IgE were found.[10] Tralokinumab treatment decreased the relative abundance of *Staphylococcus* by 38.9% (week 8) and 47.5% (week 16) compared to placebo (stable abundances).[10] *S. aureus* abundance decreased from 32% at baseline to less than 8% by week 16, a 20.7-fold decrease ($P < 0.0001$), whereas no significant decrease in *S. aureus* abundance was observed in the placebo group.[10] A 10-fold reduction in *S. aureus* abundance was noted at week 16 when comparing tralokinumab treatment to placebo in lesional skin ($P < 0.0001$).[10] Similar to other studies, the decrease in *S. aureus* abundance on lesional skin was independent of EASI-75 response, however, a greater decrease in *S. aureus* was found in tralokinumab treated patients compared to control that achieved EASI-75 responders compared to non-responders.[10] Strengths of this study include using CCL17 and other inflammatory biomarkers, the use of an anti-IL-13-only monoclonal antibody to suggest its distinct role, and a relatively large sample size.

Callewaert et al explored the impact of dupilumab on *S. aureus* colonization and reduction in EASI score compared to placebo during a 16-week trial. At baseline, lesional skin was found to have a significantly higher abundance of *S. aureus* and lower microbial diversity compared to non-lesional skin ($P < 0.05$).[23] After dupilumab treatment, *S. aureus* abundance decreased on both lesional ($P < 0.001$) and non-lesional ($P < 0.01$) skin by the first measurement at week 4 and was maintained until the end of the trial at week 16.[23] This decrease in *S. aureus* abundance was found in the

Table 1. Changes in the bacterial microbiome

Study	Treatment	Comparator	Study Design	Sample Size	Findings
Hartman et al (2023)[16]	Dupilumab	Cyclosporine, healthy control	Controlled, nonrandomized	N=415 (dupilumab=130, cyclosporine=27, healthy control=258)	Increased alpha and beta bacterial diversity in responders to dupilumab compared to baseline ($P < 0.001$), reduced abundance of *S. aureus* in lesional skin of dupilumab responders and non-responders compared to baseline (-44.9%, -38.2%, respectively, $P < 0.001$)
Olesen et al (2021)[17]	Dupilumab	Non-targeted therapy	Controlled, nonrandomized	N=44 (dupilumab=27, non-targeted therapy=17)	Increased Shannon diversity on lesional skin compared to baseline ($P = 0.005$), decreased *S. aureus* on lesional and nonlesional skin compared to baseline ($P = 0.001$, $P < 0.001$, respectively), lower proportion of *S. aureus* in dupilumab treated patients compared to non-targeted therapy ($P < 0.001$), increase in *S. epidermidis* and *S. hominis* on non-lesional skin compared to baseline ($P < 0.001$)
Simpson et al (2023)[18]	Dupilumab	Placebo	Double blind randomized control trial (6 weeks), OLE (10 weeks)	N=71 (dupilumab=45, placebo=26)	Significant improvement in SCORAD by day 14 in dupilumab ($P = 0.04$), statistical difference between dupilumab and placebo in EASI, NRS, and IGA by day 21, reduction in *S. aureus* abundance (CFUs) in dupilumab treatment by day 3 ($P = 0.02$), decrease in CCL17 in dupilumab compared to placebo ($P < 0.001$)
Umemoto et al (2024)[19]	Dupilumab	Healthy control	Controlled, nonrandomized	N=40 (dupilumab=30, healthy control=10)	94.1% decrease in *S. aureus* abundance after 12 weeks of dupilumab treatment ($P < 0.01$), increase in Shannon microbial alpha diversity index after treatment ($P < 0.01$), good correlation between EASI and *S. aureus* colonization (r^2=0/51--0.90)
Beck et al (2022)[10]	Tralokinumab	Placebo	Controlled, randomized	N=299 (tralokinumab=233, placebo=76)	20.7-fold reduction in *S. aureus* abundance at week 16 of tralokinumab treatment ($P < 0.0001$) regardless of EASI-75 response, increase in Shannon diversity index compared to placebo at weeks 8 and 16 with increase in commensal *S. epidermis*
Callewaert et al (2019)[20]	Dupilumab	Placebo	Controlled, randomized	N=54 (dupilumab=27, placebo=27)	Significant decrease in *S. aureus* abundance on lesional ($P < 0.001$) and non-lesional skin ($P < 0.01$) after 4 weeks of dupilumab, significant correlation between *S. aureus* and EASI/SCORAD scores at baseline which both decreased after week 16 of dupilumab

dupilumab group only, not placebo ($P < 0.01$).[23] However, by week 32 (post-treatment), *S. aureus* levels had returned to baseline, indicating dupilumab treatment is needed to maintain decreased *S. aureus* abundance. Similarly, alpha diversity increased in both lesional ($P < 0.001$) and non-lesional ($P < 0.05$) skin throughout the trial, with higher alpha diversity being correlated with lower *Staphylococcus* relative abundance ($P < 0.001$).[23] A significant correlation was found between EASI and SCORAD scores and *Staphylococcus* relative abundance in lesional and non-lesional skin at baseline ($P < 0.001$).[23] At week 16 post-dupilumab treatment, both EASI scores and *S. aureus* were reduced, and no difference was observed in placebo.[23] Strengths of this study include the use of a placebo control and randomization, and limitations include small sample size.

Lebrikizumab is another IL-13 inhibitor that was recently approved for the treatment of moderate-to-severe AD in patients older than 12 years.[24] While we anticipate future studies will demonstrate similar results to those seen with dupilumab and tralokinumab, peer-reviewed studies investigating lebrikizumab's effect on the skin microbiome are still needed.

DISCUSSION

All studies found that systemic treatment with biologics increased microbial diversity, measured by alpha, beta, or Shannon diversity indices, in cutaneous as well as extra-cutaneous microbiomes. Patients with AD had high relative abundances of *S. aureus* at baseline that significantly decreased post-dupilumab treatment.[19,20] Additionally, Olesen et al found that this decrease in *S. aureus* was in the dupilumab treatment group only, not the non-targeted therapy group, while Hartman et al demonstrated that dupilumab treatment resulted in a decrease in *S. aureus* colonization independent of clinical improvement.[19,20] Simi-

larly, tralokinumab treatment increased Shannon diversity index compared to placebo and significantly decreased *S. aureus* abundance independent of EASI-75 response.[10] Taken together, these studies suggest that biologics may have more direct positive effects on the microbiome, and the treatment alone, regardless of clinical improvement, decreases *S. aureus* abundance.[10,19,20]

However, in contrast to these data, Simpson et al found a correlation between decreased *S. aureus* abundance and decreased SCORAD score by day 14, and decreased EASI, NRS, and IGA scores compared to placebo by day 21 (all markers of clinical improvement).[21] This was further supported by the results from Umemoto et al, which indicated a significant correlation between decreased *S. aureus* abundance and improved EASI score.[22] Similarly, Callewaert et al observed a significant correlation between *S. aureus* abundance and EASI and SCORAD score at baseline, and by week 16 of dupilumab treatment both *S. aureus* abundance and EASI score had decreased.[23] These three studies reinforce the well-established relationship between relative *S. aureus* abundance and clinical response, as measured by symptom severity.[21-23]

Several unique findings were present in the studies included. Simpson et al demonstrated the fastest significant reduction in *S. aureus* relative abundance recorded in the literature (by day 3), as well as a significant reduction in the inflammatory cytokine CCL17 by day 3.[21] Similar to the effects of dupilumab, Beck et al observed significantly decreased *S. aureus* abundance and increase in bacterial diversity post-tralokinumab treatment compared to placebo, indicating that an IL-13 monoclonal antibody alone is sufficient for microbiome modulation in AD patients.[10] In addition to bacterial microbiome research, there is limited but promising research into the gut, nasal, and fungal microbiomes in AD patients treated with biologics. However, due to the sparse amount of data, strong claims cannot be made, and more research needs to be done.

Limitations of this review include the small sample size of the studies and the lack of control groups. Confounding factors included the use of topical corticosteroids and no clear information provided regarding other concomitant medication use. Hartman et al allowed study patients to use topicals as needed but to avoid application for 12 hours before skin swabs and examination.[19] Beck et al study methods permitted use of topical corticosteroids for participants who did meet the response criteria at week 16.[10] Patients who received rescue topical corticosteroid treatment continued tralokinumab but were considered non-responders.[10] The remaining studies did not specify if patients used concomitant treatment for atopic dermatitis, or any medication use for other medical conditions.[10,19-23] Strengths of this review include similar methodology of measuring both skin bacterial abundance and AD symptoms. Future studies should explore the mechanism between systemic therapy treatment and reduction in AD symptoms, as well as a causal relationship or mechanism between the decrease in *S. aureus* and increase in *S. epidermidis* and *S. hominis* abundance and reduction in AD symptoms.

DISCLOSURES

PL reports being on the speaker's bureau for AbbVie, Arcutis, Eli Lilly, Galderma, Hyphens Pharma, Incyte, La Roche-Posay/L'Oréal, Pfizer, Pierre-Fabre Dermatologie, Regeneron/Sanofi Genzyme, Verrica; reports consulting/advisory boards for Alphyn Biologics (stock options), AbbVie, Almirall, Amyris, Arcutis, ASLAN, Bristol-Myers Squibb, Burt's Bees, Castle Biosciences, Codex Labs (stock options), Concerto Biosci (stock options), Dermavant, Eli Lilly, Galderma, Janssen, LEO Pharma, Lipidor, L'Oréal, Merck, Micreos, MyOR Diagnostics, Regeneron/Sanofi Genzyme, Sibel Health, Skinfix, Suneco Technologies (stock options), Theraplex, UCB, Unilever, Verdant Scientific (stock options), Verrica, Yobee Care (stock options). In addition, Dr. Lio has a patent pending for a Theraplex product with royalties paid and is a Board member and Scientific Advisory Committee Member emeritus of the National Eczema Association.

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