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Biologic therapy increases Demodex density in psoriasis patients

Hasan Aksoy*, Sümeyye Altıntaş Kakşi, Öykü Gönüllü, Melek Aslan Kayıran and Vefa A. Erdemir

Department of Dermatology, Istanbul Medeniyet University Prof. Dr. Suleyman Yalcin City Hospital, İstanbul, Turkey

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Correspondence
Hasan Aksoy
Department of Dermatology
Istanbul Medeniyet University
School of Medicine
Suleyman Yalcin City Hospital
Fahrettin Kerim Gokay Street
Kadıkoy, Istanbul 34722
Turkey
E-mail: haxoil@yahoo.com

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Abstract

Background Demodex density is known to increase in various immunosuppressive conditions. The relationship between biologic therapy and Demodex density remains unknown. We aimed to investigate whether the density of Demodex mites is higher in psoriasis patients treated with biologic agents compared to treatment-naive or topically treated patients.

Methods A cross-sectional study was conducted, comparing psoriasis patients receiving biologic therapy (n = 34) with controls (n = 33). Demodex density was assessed using the standardized skin surface biopsy technique (SSSB). Statistical analysis was performed to compare the densities and prevalence of demodicosis between the two groups.

Results Demodex density was significantly higher in the biologic therapy group compared to the control group on the right cheek (7.29 vs. 0.12/cm^2; P = 0.001), left cheek (8.15 vs. 0.24/cm^2; P = 0.002), and whole face (average of all four regions: 5.50 vs. 0.80/cm^2; P = 0.001). The prevalence of demodicosis was significantly higher in the biologic therapy group on the forehead (35.3% vs. 12.1%; P = 0.043), right cheek (41.2% vs. 0%; P < 0.001), and left cheek (44.1% vs. 0%; P < 0.001). The frequency of cases with demodicosis in at least one localization was higher in the biological therapy group compared to the control group (61.8% vs. 15.2%; P < 0.001).

Conclusions Psoriasis patients receiving biologic therapy had a higher Demodex density and prevalence of demodicosis compared to controls. Biologics may lead to an increase in Demodex density by blocking specific cytokines, such as interleukin-17 and tumor necrosis factor-α, which play a role in immunity against Demodex. Further research is needed to explore the impact of different biological agents on Demodex density.

Plain Language Summary

"Demodex" mites live in human hair follicles, usually without causing any harm. However, when the immune system is suppressed due to several conditions, the Demodex density (Dd) can increase. "Biological drugs" that suppress some immunity elements are used to treat psoriasis. We aimed to determine if Dd increases in 34 psoriasis patients using biological therapies compared to those who do not.Dd on the face was significantly higher in the biological treatment group compared to the controls. The blockage of certain immune system molecules by biological drugs could explain this.

Introduction

Demodex mites, first described in 1842 by the dermatologist Gustav Simon, are commensal microorganisms that reside in clusters within the pilosebaceous units of humans.[1,2] While the two types of Demodex mites, *Demodex folliculorum*, and *Demodex brevis*, are generally harmless, they can rarely contribute to inflammatory skin diseases. Diseases associated with Demodex mites in the pilosebaceous unit are grouped under the term "demodicosis". The presence of more than five mites per square centimeter in a skin sample obtained from the lesion site using the standardized skin surface biopsy (SSSB) technique is interpreted as increased Demodex density (Dd).[3] Primary human demodicosis" can present as pityriasis folliculorum, rosacea, or Demodex abscess.[4]

Demodicosis can also occur due to various skin diseases or systemic conditions. Case series and studies have demonstrated

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that immunosuppression resulting from conditions such as leukemia and human immunodeficiency virus (HIV) infection, along with iatrogenic situations like phototherapy and topical calcineurin inhibitors, is a potential cause of an increase in Dd or demodicosis.[5–8]

In recent years, the treatment of psoriasis, a chronic inflammatory disease with complex immunological mechanisms involved in its pathogenesis, has extensively relied on biological agents targeting specific components of the immune system.[9] Although literature data indicate an increased Dd in various immunosuppressive conditions, the relationship between antipsoriatic biological agents and Dd/demodicosis remains unknown.

In clinical practice, the issue is as follows: psoriasis patients undergoing biological treatment may exhibit symptoms such as redness and dryness on their faces. Through a careful examination and superficial skin biopsy, it can be revealed that a significant portion of these cases is attributed to demodicosis. However, there is also a possibility of mistakenly interpreting the presentation as facial involvement of psoriasis and mismanaging it.

Our study aims to investigate whether the density of Demodex mites on the face is higher in psoriasis patients treated with biological agents than in treatment-naive or topically treated psoriasis patients. By assessing the impact of biological therapies on Dd, we aim to gain insights into the potential influence of these treatments on skin immunity.

Materials and methods

Study design and population

This study employed a cross-sectional design to compare the density of Demodex mites in psoriasis patients receiving biologic therapy and those who had not yet initiated any treatment or were using topical medications only. The study was conducted between May 2023 and June 2023. Ethical approval was obtained from the local ethics committee of our university (decision number: 2022/0341). A signed informed consent form was received from all subjects.

Data collection

A standardized form was used to collect demographic information and details regarding smoking and alcohol consumption habits. Additional information regarding patients' treatment regimens was recorded. Furthermore, patients were evaluated for the presence of acne, rosacea, perioral dermatitis, seborrheic dermatitis, folliculitis, blepharitis, or pityriasis folliculorum, as these conditions have been associated with an increased Dd.

Demodex density assessment

The SSSB technique is utilized to assess Dd. This technique was applied in four facial localizations, including the forehead, cheeks, and nose. The surface biopsy procedure was performed as follows: a 1 cm^2 area was marked on a glass slide using a fine ruler. The designated skin area for sampling was gently swabbed with a dry gauze pad to create mild irritation. Subsequently, one drop of cyanoacrylate adhesive was applied to the marked area on the glass slide. The glass slide was carefully pressed onto the skin, allowing the adhesive to adhere. After approximately 1 minute, the glass slide was gently lifted. The sampled area on the glass slide was examined under $\times 10$ and $\times 40$ magnification. Immersion oil was applied to enhance the visualization and determine the number of Demodex parasites within the marked area. Microscopic examination of all samples was performed by the corresponding author, who is experienced in Demodex microscopy. An increased Dd (demodicosis) was defined as the presence of five or more Demodex parasites per square centimeter of skin.

Statistical analyses

Statistical analysis was performed using the Statistical Package for the Social Sciences [SPSS] v.17 software. The threshold of 30 cases, which was considered the limit for the applicability of parametric tests, was targeted as the minimum sample size. Descriptive statistics were calculated for relevant variables, including means, standard deviations, and frequencies. The independent samples *t*-test was utilized to compare the Demodex densities, and the chi-square test was used to compare the presence of demodicosis between the two groups. $P < 0.05$ were considered statistically significant.

Results

A total of 67 psoriasis patients were included in the study, comprising 34 cases receiving biologic therapy and 33 controls, consisting of 26 patients using topical treatments and seven treatment-naive patients. A total of 268 samples were analyzed from four areas of each participant's face. The mean age of the participants was 47.52 $\pm$ 14.72, and the mean age of the two groups was similar. Although both the biological therapy group and the control group had a majority of female cases (61.8% and 60.6%, respectively), the gender distribution was comparable between the two groups. The average duration of psoriasis since diagnosis was 215.20 $\pm$ 146.41 months, and there were no significant differences in disease duration between the two groups. The agents used in the biologic therapy group were as follows: secukinumab ($n = 12$, 17.9%), ixekizumab ($n = 5$, 7.5%), ustekinumab ($n = 5$, 7.5%), adalimumab ($n = 4$, 6.0%), risankizumab ($n = 3$, 4.5%), guselkumab ($n = 3$, 4.5%), certolizumab ($n = 1$, 1.5%), and infliximab ($n = 1$, 1.5%). The average duration of biologic therapy was 31.13 $\pm$ 23.15 months.

Both groups were similar regarding the presence of clinical conditions that can be associated with demodicosis, including rosacea ($n = 9$), pityriasis folliculorum ($n = 5$), seborrheic dermatitis ($n = 4$), and folliculitis ($n = 1$). Facial involvement of psoriasis was present in 20.6% (7/34) of those using biologic agents and in 33.3% (11/33) of the control group. The two

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Table 1 Comparison of mean Demodex densities according to the localizations between the biological therapy group and the control group

Localization	Demodex density (/cm^2) (mean ± SD)		
	Biologic therapy group	Control group	*P*
Forehead	5.15 ± 9.05	2.42 ± 5.754	0.143
Nose	1.41 ± 2.78	0.42 ± 1.95	0.081
Right cheek	7.29 ± 12.72	0.12 ± 0.70	0.001*
Left cheek	8.15 ± 15.03	0.24 ± 0.74	0.002*
Average of four regions	5.50 ± 7.92	0.80 ± 1.49	0.001*

SD, standard deviation.
*$P < 0.05$.

groups had no significant differences regarding the use of topical corticosteroids, sunscreens, moisturizers, or cleansers on the face within the previous week.

In the patients treated with biologic agents, compared to controls, the Demodex mite count per square centimeter was statistically significantly higher on the right cheek (7.29 vs. 0.12/cm^2; $P = 0.001$), left cheek (8.15 vs. 0.24/cm^2; $P = 0.002$), and whole face (average of all four regions: 5.50 vs. 0.80/cm^2; $P = 0.001$). Moreover, it was numerically higher in the biological therapy group on the forehead (5.15 vs. 2.42/cm^2; $P = 0.143$) and nose (1.41 vs. 0.42/cm^2; $P = 0.081$) (Table 1). When comparing the density of Demodex folliculorum alone, the mite density in the forehead was significantly higher in the biological therapy group than in the control group (4.76 vs. 1.42/cm^2; $P = 0.039$).

When considering a mite density of above 5/cm^2 as demodicosis compared to the control group, the prevalence of demodicosis was statistically significantly higher among the biological therapy group on the forehead (35.3% vs. 12.1%; $P = 0.043$), right cheek (41.2% vs. 0%; $P < 0.001$), and left cheek (44.1% vs. 0%; $P < 0.001$), and numerically higher in the nose (14.7% vs. 3.0%; $P = 0.197$). In the biological therapy group, 61.8% (21/34) of the cases had demodicosis in at least one localization, whereas in the control group, this rate was 15.2% (5/33) ($P < 0.001$) (Table 2). Clinical characteristics and Demodex densities of those with demodicosis in at least one localization in the biological therapy group are summarized in Table 3. The detection rates of demodicosis in at least one localization according to the biologic agent used were 100.0% for guselkumab, certolizumab, and infliximab (3/3, 1/1, and 1/1, respectively), 80.0% for ixekizumab (4/5), 66.7% for risankizumab (2/3), 60.0% for ustekinumab (3/5), 50.0% for secukinumab (6/12), and 25.0% for adalimumab (1/4). Microscopic images of Demodex mites in one of the subjects in the biological therapy group can be seen in Figure 1.

Discussion

Biological therapies have been increasingly utilized to treat psoriasis in recent years. The existing literature on the safety of biological therapies has predominantly focused on bacterial, viral, and fungal pathogens. At the same time, no studies have investigated the relationship between biological therapy and Demodex, a commensal microorganism that often does not cause any clinical symptoms.

In the present study, psoriasis patients receiving biological therapy were compared to treatment-naive or topically treated psoriasis patients regarding Dd on the face. The mean Dd on the face was higher in the biological therapy group compared to the control group, and the differences were significant for cheeks and the average of four regions. The average Demodex density in the treatment-naive or topically treated psoriasis patients (0.8/cm^2) was similar to the value of 0.7/cm^2 reported for healthy adults in a previous study.[3] In contrast, the average Dd (5.5/cm^2) of four localizations in those receiving biologic therapy was distinctly high, exceeding the proposed demodicosis threshold of 5/cm^2. These findings indicate that the increase in Dd in the biologic therapy group is not only a relative increase compared to the control group but an absolute increase, and the Dd in psoriasis patients not receiving immunosuppressive treatment is not different from the general population.

We also compared the prevalence of demodicosis between the two groups by considering Dd > 5/cm^2 as demodicosis.

Table 2 The prevalence of demodicosis (Dd > 5/cm^2) according to the localizations in the biological therapy group and the control group

Demodicosis prevalence (Dd > 5/cm^2)	Forehead	Nose	Right cheek	Left cheek	At least one localization
Biological therapy group (%)	12/34 (35.3%)	5/34 (14.7%)	14/34 (41.2%)	15/34 (44.1%)	21/34 (61.8%)
Control group (%)	4/33 (12.1%)	1/33 (3.0%)	0%	0%	5/33 (15.2%)
P value	0.043*	0.197	<0.001*	<0.001*	<0.001*

Dd, Demodex density.
*$P < 0.05$.

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Table 3 Clinical characteristics and Demodex densities by region of those with demodicosis in at least one localization in the biological treatment group

Patient no	The biologic agent used	Duration of the treatment (months)	Demodex associated clinical diagnosis (if present)	Dd of forehead (/cm^2)	Dd of nose (/cm^2)	Dd of right cheek (/cm^2)	Dd of left cheek (/cm^2)	Mean Dd of four regions (/cm^2)
1	Ixekizumab	24	p.folliculorum	1	0	8	20	7.25
4	Ixekizumab	36		6	0	0	6	3.00
6	Secukinumab	11		9	0	10	8	6.75
8	Secukinumab	24		10	0	6	5	5.75
9	Secukinumab	24	Rosacea	6	1	11	16	8.50
12	Ixekizumab	24		7	0	1	0	2.00
13	Ustekinumab	48	Rosacea	1	7	13	5	6.50
15	Risankizumab	7	Rosacea	0	0	8	15	5.75
16	Secukinumab	48	p.folliculorum, seborrheic dermatitis	28	4	50	75	39.25
17	Certolizumab	18	Rosacea	23	0	22	18	15.75
18	Risankizumab	12		0	0	2	15	4.25
23	Secukinumab	42	p.folliculorum	12	0	5	0	4.25
24	Ustekinumab	24		0	7	11	14	8.00
25	Secukinumab	18		0	0	6	7	3.25
26	Ixekizumab	6		8	1	4	0	3.25
27	Guselkumab	18		6	2	0	0	2.00
28	Ustekinumab	60		0	7	8	8	5.75
29	Guselkumab	6		3	0	24	32	14.75
30	Guselkumab	60	Rosacea	41	2	40	6	22.25
32	Adalimumab	108	Rosacea	2	7	2	20	7.75
34	Infliximab	12		6	10	16	6	9.50

Dd, Demodex density; p.folliculorum, pityriasis folliculorum.

Figure 1 More than 40 Demodex mites in only one objective field detected in one of the subjects in the biological therapy group (×10)

Demodicosis rates were notably higher in three facial regions and comparatively elevated on the nose among those in the biological therapy group versus the control group. Furthermore, the proportion of individuals with demodicosis in at least one facial region was significantly greater in the biological therapy group compared to the controls. The comparable findings in nasal Demodex densities and demodicosis rates between the two groups could be attributed to the convex anatomical structure of this localization, which often hinders ideal sampling and results in decreased sensitivity.

It is worth noting that the presence of clinical conditions associated with demodicosis, such as rosacea and pityriasis folliculorum, did not significantly differ between the biological therapy group and the control group. This suggests that the observed differences in Demodex densities cannot be solely attributed to the presence of these skin conditions. Moreover, despite the increased Dd in the biologic therapy group, the lack of an increased prevalence of demodicosis-related clinical manifestations compared to the controls may be attributed to the anti-inflammatory effects of biologics. These findings of our study emphasize the need to discuss the complex relationships between Demodex mites, the immune system, and the mechanisms of action of biological agents.

Demodex mites reside in the pilosebaceous unit of the host, generally without causing any symptoms, in a balance tolerated and controlled by the host's immune system.[10] A loss of activity in the innate immune system leads to an increase in Dd without inflammation. In contrast, the increased density of the mite,

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perceived as a pathogen by the host, results in a type IV hypersensitivity reaction and the clinical presentation of papulopustular rosacea.[11] Existing literature suggests that cellular immunity is central to host defense against demodicosis. Demodex mites interact with both innate and adaptive immune system components to evade immune responses.[12]

Clinical studies and case series have shown that the occurrence of demodicosis in various conditions leads to immunosuppression. Keleş *et al.*[13] reported the development of demodicosis in three cases treated with systemic steroids and azathioprine for pemphigus vulgaris and one treated with methotrexate for psoriasis. Another study found a significantly higher prevalence of demodicosis in patients receiving phototherapy (28.9%) compared to the control group (7%). In the same study, the prevalence of demodicosis was significantly higher in patients receiving psoralen ultraviolet A (PUVA) therapy (58.3%) compared to narrow-band ultraviolet B (18.2%).[8] Gerber *et al.*[14] reported a significantly higher average Demodex density (4.7/cm^2) in 19 patients receiving epidermal growth factor receptor inhibitors compared to the Demodex density reported for the healthy adult population (0.7/cm^2). Another study divided 60 HIV-infected patients into three groups based on their CD4$^+$ cell counts and compared the presence of Demodex in eyelashes. The detection rates of Demodex were 95% in patients with CD4$^+$ count <200 cells/ml, 70% in patients with CD4$^+$ count 200–500 cells/ml, and 20% in patients with CD4$^+$ count >500 cells/ml, demonstrating an increase in the prevalence of demodicosis with decreasing CD4$^+$ cell counts.[6] Furthermore, several case series and reports document the development of demodicosis in organ transplant recipients, leukemia patients, and individuals using topical calcineurin inhibitors.[5–7,10,15] These studies and case reports represent a highly heterogeneous group in terms of diagnoses of their samples and the causes of immunosuppression, and there is no comprehensive and satisfactory explanation considering the type of immunosuppression and suggesting a mechanism for the development of the demodicosis in the relevant literature.

The biological agents used in the biological therapy group in our study were infliximab, adalimumab, certolizumab (TNF-α inhibitors), ustekinumab (IL-12 and IL-23 inhibitor), guselkumab, and risankizumab (IL-23 inhibitors), and secukinumab and ixekizumab (IL-17A inhibitors). According to the feed-forward inflammation model in psoriasis pathogenesis,[9] innate immune cells activate myeloid dendritic cells (mDC) through a group of cytokines, including TNF-α. Activated mDCs induce the differentiation of naive T cells into T-helper-17 (Th17) cells through the secretion of IL-23 and into T-helper-1 (Th1) cells through the secretion of IL-12. IL-17 secreted by Th17 cells stimulates an inflammatory cascade, leading to pathological psoriasis changes. In contrast, TNF-α secreted by Th1 cells contributes to the inflammatory cascade and activates this pathway from the beginning (Figure 2).[9] Based on this model, it can be speculated that the biological therapies used in our study are directly or indirectly involved in blocking the functions of IL-17 and TNF-α in the tissue.

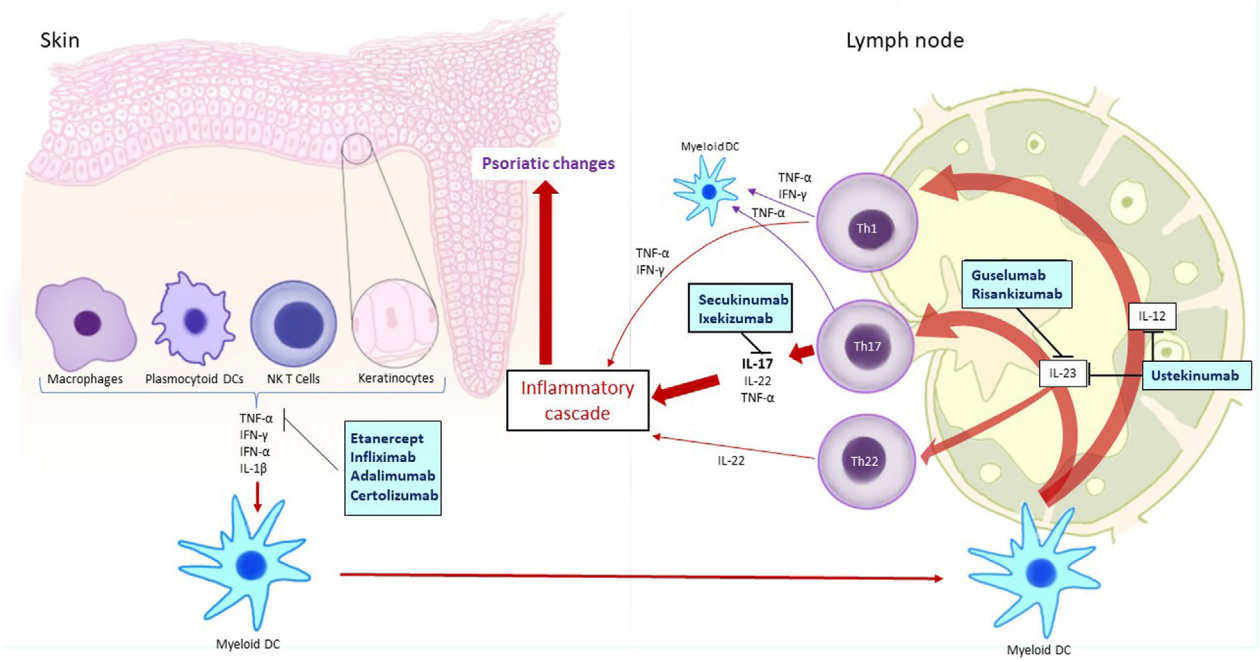

Figure 2 The feed-forward inflammation model in psoriasis and the mechanisms of action of the biologics used by the cases in our sample. The figure demonstrates that interleukin-17 (IL-17) and tumor necrosis factor-α (TNF-α) are two key cytokines whose effects are blocked by these drugs

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TNF-α is an important cytokine in the immune response against microorganisms. Experimental studies using gene-deficient mice have shown that TNF-α is a cytokine that regulates the host response to protozoal parasitic infestations. TNF-α and TNF receptors benefit the host defense against these infestations.[16] In a study where 20 patients with moderate to severe rosacea and Dd $\geq$ 15/cm^2 were treated with topical ivermectin 1% cream once daily for at least 12 weeks, both Dd and TNF-α gene expression levels significantly decreased at 6 and 12 weeks.[17] In another study comparing two cleansing gels containing 3% tea tree oil (TTO) in 49 patients with chronic blepharitis, both groups showed a decrease in Demodex presence and a significant decrease in TNF-α levels in tear samples.[18] The decrease in Demodex density and TNF-α/TNF-α gene expression levels with anti-parasitic treatments suggests that TNF-α may also play a role in the immune response against Demodex mites. This could explain the relationship between TNF-α blockade and increased Dd/demodicosis.

Another key cytokine targeted by biological therapy in our study was IL-17A. Interleukin-17 (IL-17) is a cytokine that plays a key role in host defense against various pathogens, particularly bacteria and certain fungi, in mucosal and epithelial barriers.[19] There are also clinical studies demonstrating the relationship between IL-17 and Demodex. In a study comparing cytokine levels in tear samples of 15 patients with Demodex blepharitis, Demodex-free blepharitis, and asymptomatic individuals, the IL-17 concentration in tear samples was significantly higher in the Demodex blepharitis group compared to the other two groups.[20] In another study, after treatment with TTO in 10 patients with Demodex blepharitis, there was a significant decrease in IL-17 levels in tear samples, along with clinical improvement in all patients.[21] In a previous study, Demodex folliculorum infestation has been associated with a perifollicular lymphocytic infiltration consisting of 90–95% CD4$^+$ T cells.[22] The two studies of Kim *et al*. and Kim JH *et al*.[11,20,21] suggest that the lymphocytes surrounding infested follicles could be Th17 cells, and IL-17 produced by Th17 cells may play an essential role in the immune response against Demodex mites. The Demodex-IL-17 relationship may also be related to the epithelial erosion and cutaneous fissures created during the process of Demodex penetration into the dermis.[11,23] In a study, IL-17 blockade delayed re-epithelialization in injured mouse skin, and IL-17 was shown to stimulate a specific stem cell group called Lrig1+ stem cells, located in the upper part of the pilosebaceous unit and play a central role in tissue repair.[24] Therefore, an epithelialization disorder and facilitated dermal penetration of Demodex caused by IL-17 blockade could be another explanation for the increased Dd in patients receiving biological therapy.

The limitations of our study should be acknowledged. First, the cross-sectional design limits our ability to establish a causal relationship between biological therapy and Demodex density. Longitudinal studies are warranted to investigate the dynamics of Demodex colonization in response to biological agents further. Second, the sample size of our study was relatively small, and the distribution of biological agents varied. Future studies with larger sample sizes and a more balanced representation of different biological agents would provide further insights.

In conclusion, our study demonstrated a significant increase in Demodex density and a higher prevalence of demodicosis in psoriasis patients receiving biologic therapy compared to treatment-naive or topically treated patients. These findings suggest a potential association between biological agents and Demodex mite colonization on the face. The increased Demodex density may be attributed to the immunosuppressive effects of biological agents targeting specific immune system components. The exact mechanisms underlying this association, particularly the role of cytokines such as IL-17 and TNF-α, warrant further investigation.

Understanding the relationship between immunosuppression and Demodex colonization could provide valuable insights into the complex interactions between the immune system and commensal microorganisms. Our study contributes to the growing body of evidence linking immunosuppression and Demodex colonization. By shedding light on the association between biologic therapy and Demodex density in psoriasis patients, we provide a basis for further research and potential interventions to minimize the risk of demodicosis in immunosuppressed individuals.

Patient consent

The patients in this manuscript have given written informed consent for the publication of their case details.

Data availability statement

The data supporting this study's findings are available from the corresponding author upon reasonable request.

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