ORIGINAL REPORT



# Adverse Events and Immune Response in Psoriasis Patients Receiving Interleukin-17 Inhibitors

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**Interleukin-17 inhibitors are effective in psoriasis; however, they are associated with an increased risk of infections, particularly oral candidiasis, and new-onset/flares of inflammatory bowel disease. This study aimed to identify predictive markers for these adverse events and to describe the functional immune response in patients treated with interleukin-17 inhibitors using a whole-blood stimulation system (TruCulture®). Patients with psoriasis initiating an interleukin-17 inhibitor ($n = 36$) or adalimumab ($n = 24$) were enrolled. Patients attended visits at baseline, week 12, and week 52, during which skin and mucosal swabs, and faecal and blood samples were collected. Baseline oral *Candida albicans* colonization with no clinical symptoms was associated with an increased risk of oral candidiasis during the first year of interleukin-17 inhibitor therapy, with no cases of oral candidiasis observed in the adalimumab group. Gut inflammation, measured by faecal calprotectin, remained stable in both the adalimumab and interleukin-17 inhibitor group. Colonization with *Staphylococcus aureus* did not change during treatment. It was found that interleukin-17 inhibitors induced an anti-inflammatory state and potentially more active toll-like receptor 3-mediated antiviral responses compared with adalimumab. In conclusion, screening for oral *Candida albicans* colonization prior to initiation of interleukin-17 inhibitor therapy may be a useful strategy for risk stratification and early intervention.**

*Key words:* adalimumab; candidiasis; immunity; inflammatory bowel diseases; interleukin-17; S100 proteins.

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## SIGNIFICANCE

We evaluated how psoriasis treatments that block interleukin-17 affect the immune system and investigated potential markers that could help identify patients with psoriasis at risk of certain infections and gut problems when treated. We found that interleukin-17 inhibitors had a global effect on several of the cytokine levels measured beyond interleukin-17. Furthermore, patients where we were able to measure the fungus *Candida albicans* in the mouth prior to initiating treatment were more likely to develop oral infection during treatment. This could help physicians identify patients at higher risk of this adverse event, leading to early intervention.

Psoriasis is a common chronic inflammatory skin disease driven by T helper (Th)-17 cells. Moderate-to-severe cases are often treated with biologics targeting cytokines in this pathway. Interleukin-17 (IL-17) is one of the main drivers of the disease, and four IL-17 inhibitors (IL-17i) are currently approved for treating moderate-to-severe psoriasis (secukinumab, ixekizumab, brodalumab, and bimekizumab).

IL-17i are among the biologics with the highest efficacy while also demonstrating an overall good safety profile (1). However, as with other biologics used to treat psoriasis, upper respiratory tract infections are common (2). IL-17i may also specifically impair immunity against cutaneous *Staphylococcus aureus* (*S. aureus*) and *Candida albicans* in the oral mucosa and cause flares of inflammatory bowel diseases (IBD). Indeed, IL-17 appear to promote recruitment of neutrophils, which has been shown to be important for host defence against *S. aureus* and some Gram-negative bacteria such as *Klebsiella pneumoniae* and *Bordetella pertussis* (3, 4). Furthermore, patients with rare inborn mutations in the IL-17RA and IL-17F gene have impaired mucocutaneous immunity to *Candida albicans* (5). Consistent with this, oral candidiasis has frequently been reported in clinical trials of IL-17i, particularly bimekizumab, with 19.3% developing oral candidiasis in a phase III clinical trial (2, 6). IL-17 does not appear to be as important for immunity against vulvovaginal candidiasis. Instead, it is thought that vulvovaginal candidiasis is caused by neutrophil dysfunction (7). Indeed, the incidence of genital candidiasis is much lower than that of oral candidiasis in clinical

trials of IL-17i (2). Furthermore, IL-17 is important for immunity against other fungi such as *Malassezia* and dermatophytes (8).

Upstream inhibition of the Th17 pathway with IL-12/23p40 and IL-23p19 inhibitors is effective in both psoriasis and IBD (9); however, patients had no improvement and some experienced worsening of Crohn's disease in phase II trials of secukinumab and brodalumab (10, 11). New-onset IBD has also been observed in psoriasis trials of IL-17i (12). This contradictory finding has been explained by the importance of IL-17A for intestinal barrier integrity. In contrast, inhibition of upstream IL-23 does not affect IL-17A production from innate lymphocytes. The activation of pathogenic Th17 cells is also inhibited by blocking IL-23 (13).

While the risk of cutaneous *S. aureus* infection, oral candidiasis, and new-onset/flare of IBD appears to be directly related to the specific inhibition of IL-17, secondary effects on the immune system are likely. For example, reduced IL-10 has been reported in psoriasis patients treated with IL-17i who experienced *Candida* infections during therapy (14). Investigating the overall effect on the immune system of specific IL-17 inhibition may help explain why the overall infection risk appears to be unchanged in patients treated with IL-17i versus adalimumab (15). Adalimumab functions by inhibiting tumour necrosis factor (TNF) and is associated with an increased risk of infections including reactivation of latent tuberculosis. However, the immunological mechanisms are not fully understood (16, 17). Adalimumab is commonly used as first-line biologic therapy for patients with psoriasis in Denmark. It therefore serves as a relevant reference when evaluating differences in the safety profile of biologics used to treat psoriasis.

Identifying patients at risk of adverse events is crucial, as it allows for implementation of preventive measures or selection of biologics targeting alternative pathways. This study aimed to identify markers that predict an increased risk of cutaneous *S. aureus* infections, oral candidiasis, or IBD in psoriasis patients treated with IL-17i versus those treated with adalimumab, while also assessing the impact of IL-17i on the functional immune response.

## MATERIALS AND METHODS

This cohort study was conducted in accordance with the Declaration of Helsinki and was approved by the Danish Data Protection Agency (P-2021-363) and a scientific ethics committee for the Capital Region of Denmark (H-21022377). All included patients gave written informed consent and did not receive any compensation. The study is reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines for cohort studies (18).

### *Setting and patients*

We recruited patients with plaque-type psoriasis from the outpatient clinic at the Department of Dermatology and Allergy, Copenhagen University Hospital – Herlev and Gentofte between March 2022 and March 2024. Eligible participants were patients with psoriasis initiating an IL-17i without prior exposure to any IL-17i and, as controls, patients initiating treatment with adalimumab. Patients were excluded if they were pregnant, breast-feeding, or under 18 years of age.

### *Measurements and outcomes*

Patients enrolled in the study attended visits at baseline (treatment initiation), week 12, and week 52 in conjunction with regular outpatient visits. At each visit, enrolled patients were asked about adverse events and a fixed set of gastrointestinal questions, some of which were adapted from the Harvey-Bradshaw index for Crohn's disease (Table SI). At each visit, we also collected skin and mucosal swabs (eSwab Collection and Transport System, Copan Italia, Brescia, Italy), and faecal and blood samples.

A detailed description of the analyses of the collected samples is provided in Appendix S1.

In short, oral mucosal and perianal skin swabs were collected to identify *Candida* species colonization. Swabs were collected from the nasal vestibule, retroauricular skin, umbilicus, and perineum to identify *S. aureus* colonization. Of note, we updated the study protocol mid-study, therefore we collected samples for *S. aureus* colonization only from a subset of patients. Colonization was defined as being culture positive without having clinical symptoms. Oral candidiasis was diagnosed clinically without culture confirmation.

Faecal samples were tested for faecal calprotectin (FCP) and used as a surrogate marker of gut inflammation (19). We used a method with a reference change value of 150%, meaning that variation between samples below this threshold may be due to test variation. An FCP $\geq$ 50 µg/g was considered elevated.

Blood was transferred to TruCulture® tubes to mimic the immune response to various stimuli. In each tube, concentrations of TNF-α, interferon (IFN)-α, IFN-γ, IL-1β, IL-6, IL-8, IL-10, IL-12p40, and IL-17A were measured.

### *Statistical methods*

The association between oral *Candida* colonization and oral candidiasis the first year was tested using Fisher's exact test. Cytokine concentrations measured by the TruCulture® assay at baseline and at week 12 were compared using the Wilcoxon signed-rank test. *P*-values $<0.05$ were considered significant. R statistical software version 4.2.0 (R Foundation for Statistical Computing, Vienna, Austria) was used for data analysis (20).

**Table I. Baseline characteristics**

| Baseline characteristics | Adalimumab group ($n=24$) | IL-17i group ($n=36$) | $p$-value |
|---|---|---|---|
| Female sex, *n* (%) | 11 (45.8) | 10 (27.8) | 0.25 |
| Age, years, mean (SD) | 48.9 (17.1) | 47.8 (14.7) | 0.79 |
| BMI, kg/m$^2$, mean (SD) | 31.5 (9.7) | 28.8 (6.6) | 0.20 |
| Smoking *n* (%) | | | 0.40 |
| Smoker | 3 (12.5) | 9 (25.0) | |
| Previous smoker | 11 (45.8) | 17 (47.2) | |
| Never smoker | 10 (41.7) | 10 (27.8) | |
| Psoriatic arthritis *n* (%) | 4 (16.7) | 7 (19.4) | 1 |
| Bio-naive, *n* (%) | 21 (87.5) | 1 (2.8) | <0.001 |
| Baseline PASI, median (IQR) | 8.1 (3.7–12.2) | 7.0 (4.6–12.6) | 0.71 |

*P*-values are from an ANOVA (continuous variables) or $\chi^2$/Fisher's exact test as appropriate (categorical variables).
BMI: body mass index; IL: interleukin; IQR: interquartile range; PASI: Psoriasis Area and Severity Index; SD: standard deviation.

## RESULTS

A total of 58 patients were included in the study. Two patients never started treatment and four patients initially enrolled in the adalimumab group and, after failing treatment, were subsequently enrolled in the IL-17i group. Thus, the study population comprised 56 patients and 60 treatment series, 24 in the adalimumab group and 36 in the IL-17i group (18 ixekizumab and 18 bimekizumab). Baseline characteristics are presented in **Table I** and responses to fixed questions at each visit are summarized in Table SI. None of the patients had a family history of IBD.

In the adalimumab group, 21 (87.5%) had a 12-week visit and 16 (66.7%) had a 52-week visit. In the IL-17i group, 30 (83.3%) had a 12-week visit and 24 (66.7%) had a 52-week visit. Reasons for dropout were primary ineffectiveness ($n=5$), adverse events ($n=3$), paused treatment ($n=2$), administrative loss ($n=1$), withdrawal of consent ($n=4$), and missed follow-up ($n=5$).

### *Colonization with Candida species*

At baseline, 9/24 (37.5%) in the adalimumab group and 13/36 (36.1%) in the IL-17i group were colonized with *Candida* species in the oral cavity. None in the adalimumab group developed oral candidiasis during the first year of treatment. In the IL-17i group, 6/36 (16.7%) developed oral candidiasis: 2/23 (8.7%) of non-colonized and 4/13 (30.8%) of colonized patients (**Table II**). However, this was not statistically significant ($p$-value: 0.16). Patients who developed oral candidiasis in the colonized group were all colonized with *Candida albicans* at baseline, while none colonized with *Candida glabrata* ($n=2$) or *Candida dubliniensis* ($n=1$) developed oral candidiasis. Thus, when restricting the analysis to patients colonized with *Candida albicans* at baseline, 4/10 (40%) developed oral candidiasis, which was statistically significant from the non-*Candida albicans* colonized group at baseline where 2/26 (7.7%) developed oral candidiasis ($p$-value=0.04). As previously mentioned, oral candidiasis was diagnosed clinically without culture confirmation and none led to treatment discontinuation.

**Table II. Oral colonization with *Candida* and candidiasis**

| Group | Colonized at 12 weeks | Colonized at 52 weeks | Oral candidiasis |
|---|---|---|---|
| Adalimumab group | | | |
| Not colonized at baseline | 3/13 (23.1) | 2/10 (20.0) | 0/15 (0.0) |
| Colonized at baseline | 8/8 (100.0) | 3/6 (50.0) | 0/9 (0.0) |
| IL-17i group | | | |
| Not colonized at baseline | 5/18 (27.8) | 6/14 (42.9) | 2/23 (8.7) |
| Colonized at baseline | 7/11 (63.6) | 5/10 (50.0) | 4/13 (30.8)[a] |

[a]All 4 cases were colonized with *Candida albicans* at baseline. In total, 10 were colonized with *Candida albicans* at baseline, meaning 40% (4/10) of the patients colonized at baseline developed oral candidiasis.
This table shows the prevalence of oral *Candida* colonization at baseline. Data are presented as no. (%) of patients with positive colonization at week 12 or week 52 or oral candidiasis in the first year.

Table II indicates the association between oral colonization at baseline and colonization at follow-up visits. Colonization status varied between visits, with many patients switching between being culture positive and negative during follow-ups (Table II). Because only 1/33 were colonized with *Candida* species on the perianal skin, we did not proceed with further analysis.

### *Colonization with S. aureus*

At baseline, 5/12 (41.7%) in the adalimumab group and 8/15 (53.3%) in the IL-17i group were colonized with *S. aureus* at any of the 4 body sites (nasal vestibule, retroauricular skin, umbilicus, and perineum). We did not observe any cases of infection suspected to be caused by *S. aureus*. Table SII shows the association between baseline *S. aureus* colonization and colonization at follow-up visits. *S. aureus* colonization was highly variable between visits and colonization was assessed in a very limited number of patients.

### *Subclinical gut inflammation*

In the adalimumab group, 8/21 (38.1%) sent a faecal sample at both baseline and week 12, while 7/16 (43.8%) provided a faecal sample at both baseline and week 52 (**Table III**). None experienced significantly increased FCP during treatment.

In the IL-17i group, 18/30 (60.0%) sent a faecal sample at both baseline and week 12, while 16/24 (66.7%) provided a faecal sample at both baseline and week 52 (Table III). One patient had a significant increase in FCP after 12 weeks (from <15 µg/g to 64 µg/g), which decreased to <15 µg/g after 52 weeks. Another patient's FCP level increased from 66 µg/g at baseline to 398 µg/g at 52 weeks. The patient was asymptomatic and a subsequent FCP test 4 weeks later was normal (45 µg/g). In general, most patients maintained a low FCP during both treatments (< 50 µg/g).

### *Functional immune response*

Blood samples from a subset of 11 patients were used to examine the functional innate immune response.

**Table III. Change in f-calprotectin over time**

| | Baseline → Week 12 | |
|---|---|---|
| F-calprotectin | Adalimumab ($n=8$) $n$ (%) | IL-17 ($n=18$) $n$ (%) |
| Baseline | | |
| < 50 µg/g | 6 (75.0) | 16 (88.9) |
| ≥ 50 µg/g | 2 (25.0) | 2 (11.1) |
| Week 12 | | |
| < 50 µg/g | 8 (100.0) | 16 (88.9) |
| ≥ 50 µg/g | 0 (0.0) | 2 (11.1) |
| Change in f-calprotectin[a] | | |
| Significant decrease | 1 (12.5) | 0 (0.0) |
| No significant change | 7 (87.5) | 17 (94.4) |
| Significant increase | 0 (0.0) | 1 (5.6) |
| | Baseline → Week 52 | |
| F-calprotectin | Adalimumab ($n=7$) $n$ (%) | IL-17 ($n=16$) $n$ (%) |
| Baseline | | |
| < 50 µg/g | 7 (100.0) | 14 (87.5) |
| ≥ 50 µg/g | 0 (0.0) | 2 (12.5) |
| Week 52 | | |
| < 50 µg/g | 7 (100.0) | 14 (87.5) |
| ≥ 50 µg/g | 0 (0.0) | 2 (12.5) |
| Change in f-calprotectin[a] | | |
| Significant decrease | 1 (14.3) | 1 (6.3) |
| No significant change | 6 (85.7) | 14 (87.5) |
| Significant increase | 0 (0.0) | 1 (6.3) |

[a]The test has a reference change value of 150%. Thus, a significant decrease corresponds to ≤ 40% of the original value, and a significant increase corresponds to ≥ 250% of the original value.

All 11 patients initiated ixekizumab; 10 switched from adalimumab to ixekizumab, of whom 9 had no washout period and 1 had a short washout period (6 weeks). The last patient switched from ustekinumab to ixekizumab without a washout period. Absolute Psoriasis Area and Severity Index (PASI) <4 was achieved by 8/11 (72.7%) patients at week 12.

The induced cytokine release at baseline and week 12 are visualized in **Fig. 1**. LPS-induced (TLR4) IFN-γ, IL-12 and IL-6 decreased, while IL-10 increased (Fig. 1A). R848-induced (TLR7/8) IL-12 and IL-6 decreased (Fig. 1B). Poly I:C-induced (TLR3) IFN-α, IL-1β, and TNF-α increased (Fig. 1C). Anti-CD3/CD28-induced (T-cell stimulation) IL-17A and IL-6 decreased (Fig. 1D). Lastly, the cytokines of the unstimulated samples did not change (Fig. 1E).

A sub-analysis conducted on the 6 patients who switched from adalimumab to ixekizumab without a washout period and with an acceptable treatment effect (absolute PASI <4) was consistent with the main analysis.

## DISCUSSION

In this clinical cohort study, we investigated markers in patients with psoriasis that may predict who is at risk of adverse events with IL-17i. We also described the effect of IL-17i on the functional immune system. Our main finding was that oral *Candida albicans* colonization prior to treatment initiation with IL-17i increased the risk of oral candidiasis in the first year (40.0% vs 7.7%). We also found an altered innate immune response 3 months after initiation of an IL-17i beyond the expected reduction in IL-17 levels.

*Candida* colonization is common in psoriasis. We found that 37% were colonized with *Candida* species in the oral mucosa. This is consistent with a study by Elsner et al., who found 47% of patients with psoriasis to be colonized compared with 20% of healthy controls but found no association between colonization and disease severity (21). Others have shown an association between oral candidiasis and disease severity, emphasizing the need to distinguish between colonization and infection (22). Although oral candidiasis is not life-threatening, it can cause discomfort and affect well-being, and, if associated with exacerbation of psoriasis, the identification of those patients at risk of oral candidiasis may have important clinical significance. Our study suggests that oral *Candida albicans* colonization, as determined by a simple oral swab, was associated with a much higher risk of oral candidiasis (40.0% vs 7.7%) in patients treated with IL-17i. This easy-to-perform test could be helpful in the clinic to help stratify biologic treatment or antifungal prophylaxis could be considered in the early stages of treatment, when the risk of oral candidiasis is highest (23). Of note, *Candida albicans* are diverse, and different strains exhibit varying virulence (24). Testing for specific strains could provide additional insight but would require extensive testing.

The study also investigated whether FCP, as a marker of subclinical gut inflammation, increased during IL-17i treatment as new-onset/flare of IBD is a potential IL-17i specific adverse event. Although the number of samples analysed was small, we did not find any signal to suggest that FCP increased during therapy. This result contrasts with that of an Italian study, in which 2/83 patients with psoriasis treated with IL-17i had a significant increase in FCP over 24 weeks leading to a diagnosis of ulcerative proctitis and Crohn's disease. In the same study, no increase was seen in the 39 patients treated with IL-23i (25). Psoriasis and IBD share the IL-23/Th17 axis, and psoriasis patients have an increased prevalence of IBD (26). Therefore, it is not known whether these patients would have developed the disease even if they had not been treated with an IL-17i. Indeed, it is unclear whether IL-17i cause incident IBD, as they do not appear to confer an increased risk of incident IBD compared with placebo (27).

We investigated the functional immune response in 11 patients treated with the IL-17 inhibitor ixekizumab before and 3 months after treatment initiation using whole-blood stimulation, which has the advantage over stimulation of peripheral blood mononuclear cells (PBMCs) as it is more reproducible and better reflects the natural immune response (28). All but 1 patient switched from adalimumab to ixekizumab (the last patient switched from ustekinumab) without sufficient washout periods and, accordingly, TNF-α increased after discon-

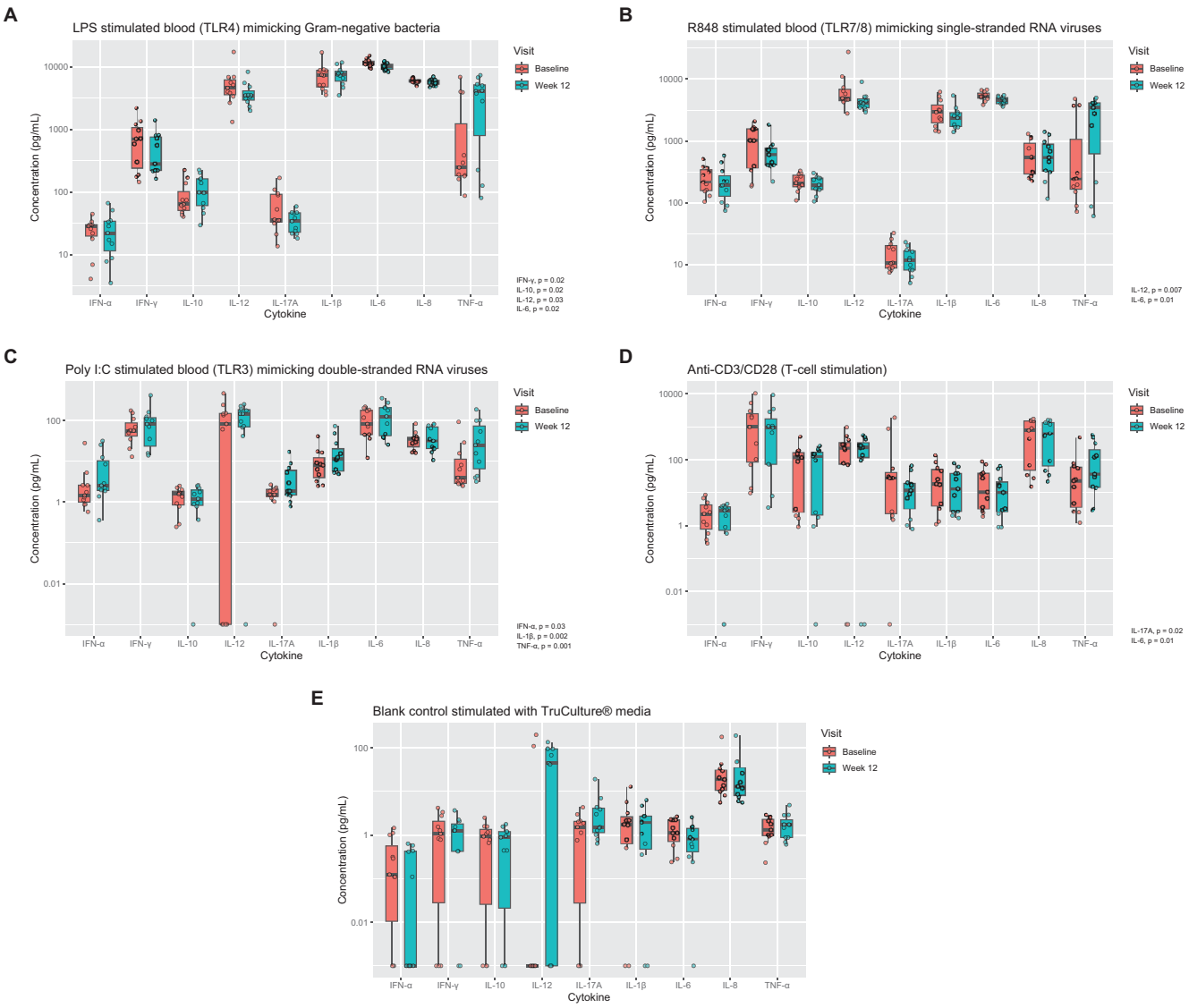


**Fig. 1. Functional immune response.** Box plots of induced cytokine concentrations in 11 patients treated with ixekizumab following stimulations that mimic activation of (A) toll-like receptor (TLR)4, (B) TLR7/8, (C) TLR3 as well as a tube with (D) T-cell stimulation, and (E) a blank control. Cytokine concentrations were measured before and 3 months after treatment initiation using whole-blood stimulation.

tinuing adalimumab. We found that IL-17A decreased after T-cell stimulation, which is consistent with the mechanism of action of ixekizumab.

A previously published study recruiting patients with psoriasis from the same department as the present study also investigated the functional immune response by TruCulture® in patients initiating adalimumab and, as expected, TNF-α decreased with all stimuli (16). We found notable differences between patients treated with adalimumab and those treated with ixekizumab, which varied depending on the specific TLR pathway activated.

Following TLR4 stimulation, the proinflammatory cytokines IL-6, IL-12, and IFN-γ decreased, whereas the anti-inflammatory cytokine IL-10 increased in the ixekizumab group, suggesting a shift towards a more anti-inflammatory state. In contrast, both the proinflammatory cytokine IL-1β and the anti-inflammatory cytokine IL-10 decreased in the adalimumab group, indicating a more generalized suppression of the innate immune system compared with ixekizumab (16).

Following TLR7/8 stimulation, IL-6 and IL-12 levels decreased in the ixekizumab group, whereas the adalimumab group showed a decrease in IL-8 and an increase in IL-1β and IL-12 (16). This suggests that adalimumab reduces acute inflammation while maintaining Th1 induction by IL-1β and IL-12, whereas ixekizumab broadly attenuates innate immune activation not only by IL-17A but also by upstream IL-12 and IL-6, which induce Th1 and Th17 differentiation, respectively (29, 30). IL-6 inhibition is ineffective in the treatment of plaque psoriasis, which has been speculated to be due to a compensatory increase in other proinflammatory cytokines (29). However, following short-term ixekizumab

treatment, we found decreased IL-6 but no compensatory increase in measured proinflammatory cytokines.

The most striking difference was observed following TLR3 stimulation with poly I:C. In the ixekizumab group, IFN-α and IL-1β levels increased after initiation, whereas (non-significant) decreases in IFN-α and IFN-γ were observed in the adalimumab group (16). These results suggest that ixekizumab may enhance antiviral immunity compared with adalimumab. TLR3 recognizes double-stranded RNA viruses and therefore has the potential to recognize multiple viruses, as double-stranded RNA is an intermediate product in RNA and DNA virus replication (31). However, in the adalimumab vs ixekizumab clinical trial in psoriatic arthritis, the overall risk of (bacterial and viral) infections was numerically higher with ixekizumab (42% vs 39%) (15). In contrast, IL-17i has been associated with both a lower and higher risk of infectious disease compared with TNFi in observational studies (32, 33). No apparent difference in the overall risk of infection between IL-17i and TNFi may be explained by the fact that individuals with inborn defects of the TLR3 pathway only show increased susceptibility to herpes simplex type 1 (HSV-1) encephalitis (31). Interestingly, a previous Danish study showed a lower incidence of alphaherpesvirus infection (which includes HSV-1) in patients treated with IL-17i versus TNFi (34). Thus, IL-17i may enhance antiviral responses against HSV-1 via TLR3, potentially explaining the lower incidence of alphaherpesvirus infections observed compared with TNFi.

Our study is limited by the small sample size, and as IBD development is rare the findings on subclinical gut inflammation should be interpreted with caution. However, we found no evidence of increased subclinical gut inflammation in patients treated with IL-17i. Regarding the risk of oral candidiasis, we were limited by our reliance on a clinical diagnosis, which introduces the risk of confirmation bias, as IL-17i is known to be associated with an increased risk of oral candidiasis. Nevertheless, our findings of a much higher risk of oral candidiasis when colonized with *Candida albicans* in patients treated with IL-17i are interesting and warrant further investigation. Strengths of our study include the thorough characterization of the enrolled patients, the use of a comparison group, and the prospective design.

In conclusion, we explored potential markers that could help identify patients at increased risk of adverse events during IL-17i therapy. We found that oral *Candida albicans* colonization prior to treatment initiation may serve as a predictor for risk of developing oral candidiasis within the first year. In addition, we observed that IL-17i induces a more anti-inflammatory state and a potentially more effective antiviral response via TLR3 compared with TNFi. However, it is important to note that the overall risk of infection does not appear to be lower with IL-17i compared with TNFi.

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