2 Lott JP, Narayan D, Soulos PR, Aminawung J, Gross CP. Delay of surgery for melanoma among medicare beneficiaries. *JAMA Dermatol* 2015; **151**: 731–741.
3 Niehues NB, Evanson B, Smith WA, Fiore CT, Parekh P. Melanoma patient notification and treatment timelines. *Dermatol Online J* 2019; **25**:13030/qt0x15j2dk.
4 Damato EM, Damato BE. Detection and time to treatment of uveal melanoma in the United Kingdom: an evaluation of 2384 patients. *Ophthalmology* 2012; **119**: 1582–1589.
5 McKechnie AJ. See-and-treat surgery for facial skin cancer. *Br J Oral Maxillofac Surg* 2014; **52**: 598–602.
6 Wehner MR, Dalma N, Landefeld C *et al*. Natural history of lesions suspicious for basal cell carcinoma in older adults in Ikaria, Greece. *Br J Dermatol* 2018; **179**: 767–768.
7 Alam M, Goldberg LH, Silapunt S *et al*. Delayed treatment and continued growth of nonmelanoma skin cancer. *J Am Acad Dermatol* 2011; **64**: 839–848.
8 Valenti M, Pavia G, Gargiulo L *et al*. Impact of delay in follow-up due to COVID-19 pandemic on skin cancer progression: a real-life experience from an Italian hub hospital. *Int J Dermatol* 2021; **60**: 860–863

DOI: 10.1111/jdv.17950

Successful treatment of psoriasis with adalimumab induced no changes in the gut microbiota

To the Editor,

Patients with psoriasis display a distinct gut microbiota compared with healthy.[1] However, studies examining the potential modulatory treatment effects for psoriasis on the gut microbiota in patients with psoriasis are scarce. We conducted a pilot-study to investigate the effect of the TNF-α-inhibitor, adalimumab, on the gut microbiota in patients with psoriasis.

Faecal samples were collected from 10 patients with psoriasis before initiation of adalimumab and a second sample was collected after a successful clinical response. Using metagenomic shotgun sequencing the gut microbiota was compared before and after treatment. In addition, the gut microbiota after treatment was compared with samples from a large group of age, gender, body-mass-index-matched healthy controls collected at our department. In addition, the gut microbiota after treatment was compared with samples from a large group of age, gender, body-mass-index-matched healthy controls collected at our department (submitted for publication).

Baseline PASI was 10.2 (IQR 8.2, 11.5), and after a median of 5.5 (IQR 3.2–7.8) months of treatment, the median PASI was 0.0 (0.0, 1.03) (Table 1).

The gut microbiota displayed no significant changes in taxonomic richness or in diversity of metagenomic species (MGS)

Table 1 Baseline demographics in patients with psoriasis

	Psoriasis (n = 10)	Healthy controls (n = 52)
Age, year, median (IQR)	36.0 (25.0–44.0)	49.0 (36.0–58.0)
Gender, n, male (%)	6 (60.0)	29 (55.8)
BMI, kg/m^2, median (IQR)	23.4 (21.7–25.5)	24.7 (22.9–27.2)
Psoriasis specific characteristics, median (IQR)		
PASI, baseline before treatment	10.2 (8.2–11.5)	
PASI, after 3–9 months of adalimumab treatment	0.0 (0.0, 1.03)	–
Age at debut, years	15.0 (7.0–20.0)	–
Time since debut, years	14.0 (7.0–33.0)	–
Ongoing psoriasis treatment, n (%)		
None/emmolients	5 (50.0)	–
Topical corticosteroids ± vitamin D	5 (50.0)	–
Family history of psoriasis		
Yes	2 (20.0)	–
No	8 (80.0)	–
Comorbidities, n (%)		
Psoriatic arthritis	1 (10.0)	–
Active or history of parodontitis	1 (10.0)	8 (15.4)
Hypertension	0 (0.0)	2 (3.8)
Treatment, n (%)		
Time since antibiotic treatment, years, median (IQR)	2.5 (1.4–5.0)	3.0 (1.0–5.0)
Motility affecting	0 (0.0)	0 (0.0)
Statins	0 (0.0)	3 (5.8)
Other non-systemic anti-inflammatory	0 (0.0)	2 (3.8)
Antidepressants	0 (0.0)	1 (1.9)
Proton-pump-inhibitors	0 (0.0)	0 (0.0)
Smoking, n (%)		
Yes	1 (10.0)	3 (5.8)
Former	3 (30.0)	12 (23.1)
No	6 (60.0)	37 (71.2)
Use of alcohol (units per week), n (%)		
0	2 (10.0)	11 (21.29)
1–7	7 (10.0)	30 (57.7)
8–14	0 (0.0)	8 (15.4)
15–21	1 (10.0)	2 (3.8)
>21	0 (0.0)	1 (1.9)
Level of physical activity, n (%)		
Low	3 (30.0)	3 (5.8)
Moderate	4 (40.0)	30 (57.7)
High	3 (30.0)	19 (36.5)
Dietary habits, n (%)		
Unhealthy	0 (0.0)	3 (5.8)
Medium	7 (70.0)	34 (65.4)
Healthy	3 (30.0)	15 (28.8)
Paraclinical test, (mg/L), median (IQR)		
High-sensitivity C-reactive protein (mg/L)	0.9 (0.3–1.3)	0.9 (0.3–1.5)

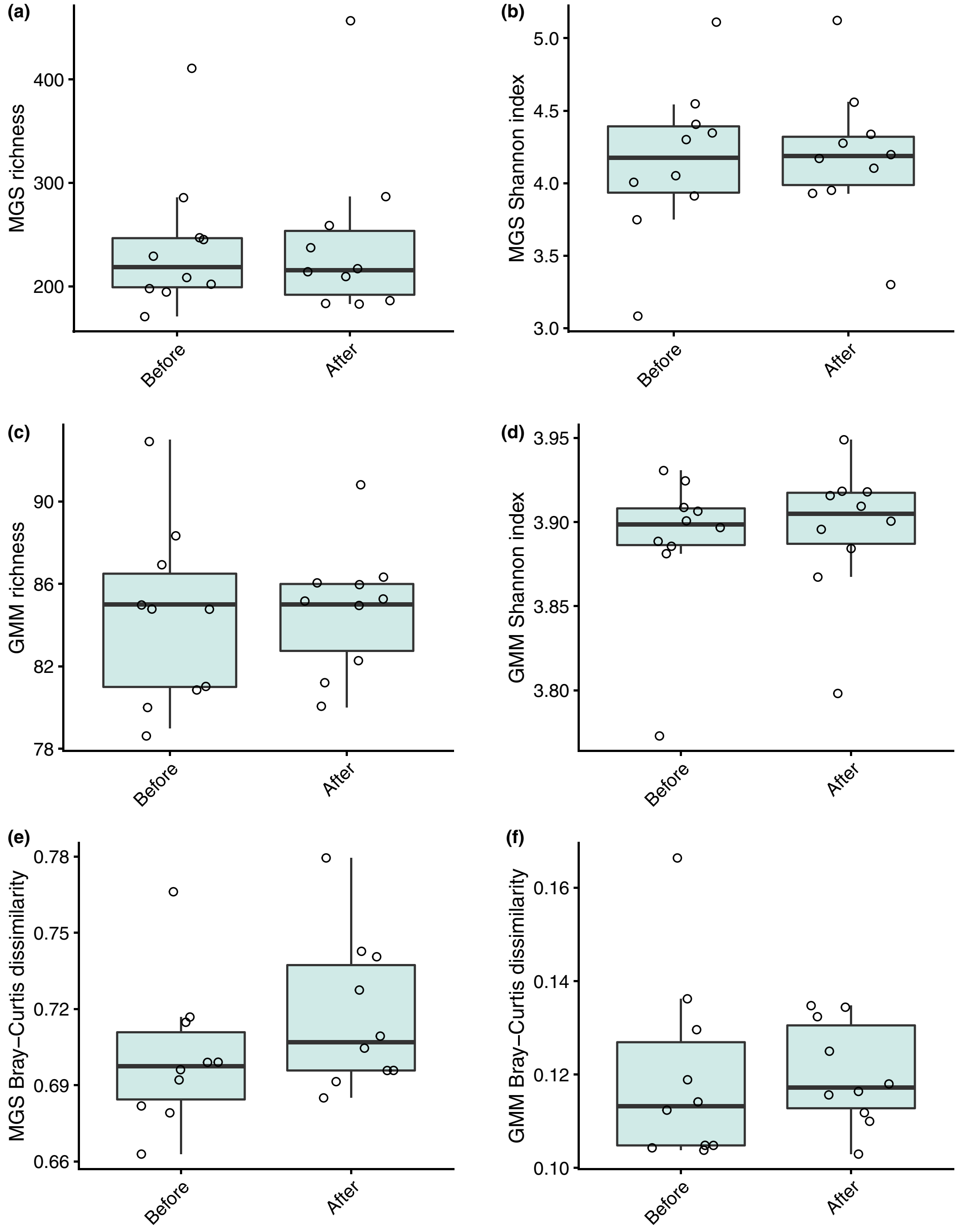

Figure 1 (a–d) The gut microbiota of patients with psoriasis ($n = 10$) did not differ in (a) richness of MGS ($P = 1.00$), in (b) diversity of MGS ($P = 0.77$), in (c) richness of GMM ($P = 0.79$) or in (d) diversity ($P = 0.92$) of GMM when comparing before and after treatment with adalimumab. Boxplots displaying microbial α-diversity assessed as richness and diversity (Shannon diversity index) of metagenomic species (MGS) and of gut metabolic module (GMM). (e,f) Adalimumab had no impact on community composition of (e) metagenomic species (MGS) ($P = 0.28$) or (f) gut metabolic modules (GMM) ($P = 0.65$) when comparing samples before and after treatment in patients with psoriasis ($n = 10$). The gut microbiota after treatment with adalimumab did not demonstrate a shift in the community composition of (e) MGS or (f) GMM becoming more similar to that of the healthy controls (healthy controls represented as the reference on the x-axis). Boxplots displaying changes in overall community composition of MGS and GMM assessed by Bray-Curtis dissimilarities

after treatment with adalimumab compared with baseline (Fig. 1a,b). Neither a difference in MGS nor in diversity of gut metabolic modules (GMM) could be observed following treatment (Fig. 1c,d).

The species, which displayed the largest difference in abundance after treatment, were *Gemmiger formicilis*, *Fusicatenibacter saccharivorans*, *Roseburia faecis and Pseudoflavonifractor sp.*, all showing a reduced abundance, whereas *Streptococcus thermophilus*, *Ruminococcaceae sp.*, *Lachnospiraceae bacterium and Clostridiales sp*. displayed an increased abundance after treatment; however, after multiple testing, none of the changes were significant. The GMM for alanine degradation displayed an increased abundance while the GMM for ribose and lactaldehyde degradation showed a decreased abundance following treatment with adalimumab; however, none of the GMMs remained significant after multiple testing. When examining community composition, after treatment patients did not demonstrate a shift of MGS or GMM becoming more similar to that of the healthy controls (Fig. 1e,f).

In this study, adalimumab in patients with psoriasis did not change the gut microbiota; thus, a profile of what is seen in the healthy individuals could not be observed.

Valentini et al. examined the gut microbiota in patients with psoriasis, treated with adalimumab or golimumab or ustekinumab ($n = 10$) and compared the outcome with untreated patients with psoriasis ($n = 20$),[2] and found that the gut microbiota of the treated group displayed a different profile. However, the drug heterogeneity might have confounded the results.[3,4]

Yeh et al. characterized the gut microbiota in patients with psoriasis treated with secukinumab ($n = 24$), ustekinumab ($n = 10$) and in healthy controls ($n = 12$), where samples were collected prior to treatment and after 3 and 6 months, respectively, of treatment.[5] Although none of the treatments induced changes in α-diversity, a significant alteration in β-diversity was seen in the secukinumab group, but not in the ustekinumab group indicating different effect of different treatment target on the gut microbiota.

This has been supported by another study investigating the effect on an IL-17A- and a TNF-α-inhibitor on the gut microbiota in patients with spondylarthritis.[6] Here, the IL-17A-inhibitor group ($n = 14$) displayed significant alteration of the gut microbiota shifting towards a fungal dominance and intestinal inflammation, whereas this could not be observed in the TNF-α-inhibitor group ($n = 15$). The findings support our findings of less influence of TNF-α-inhibitors on the microbiota. Thus, the available data may overall suggest that biologic treatments show large variability in their effect on the gut microbiota.

Treatment with adalimumab in patient with psoriasis did not alter the gut microbiota despite achievement of an excellent clinical response; however, results should be validated using larger groups and different treatment arms. This could expand knowledge of the potential impact of biologic treatment on the gut microbiota.

Conflict of interest

TT has been an investigator for Novartis, Abbvie, Dr. Wolff, Galderma and Almirall. AE has received research funding from Pfizer, Eli Lilly, Novartis, Bristol-Myers Squibb, AbbVie, Janssen Pharmaceuticals, the Danish National Psoriasis Foundation, the Simon Spies Foundation and the Kgl Hofbundtmager Aage Bang Foundation, and honoraria as consultant and/or speaker from AbbVie, Almirall, Leo Pharma, Galápagos NV, Sun Pharmaceuticals, Samsung Bioepis Co., Ltd., Pfizer, Eli Lilly and Company, Novartis, Galderma, Dermavant, UCB, Mylan, Bristol-Myers Squibb and Janssen Pharmaceuticals. CZ has been an advisor, investigator and speaker for Abbvie, Eli Lilly, Novatis, Sanofi, Leo pharma, UCB, CSL and Almirall. LS has been an advisor, investigator and speaker for Abbvie, Eli Lilly, Novartis, Sanofi, Celegene, Leo pharma, BMS, UCB and BI outside the submitted work. LS reports non-financial support from Abbvie, Sanofi, Janssen and grants from Novartis, Janssen, BMS and Sanofi. The Novo Nordisk Foundation Center for Basic Metabolic Research is an independent research centre at the University of Copenhagen that is partially funded by an unrestricted donation from the Novo Nordisk Foundation. The funding sources had no role in the study design, data collection, data analysis, data interpretation or writing of the manuscript.

Funding sources

This study was supported by Aage Bangs Foundation, Roberts Wehnerts and Kirsten Wehnerts Foundation, Liv Bryhns Foundation, Grosserer Fogts Foundation, The LEO Foundation and The Novo Nordisk Foundation Center for Basic Metabolic Research.

Data availability statement

Data are available upon request.

T. Todberg,[1,2,*] A. Egeberg,[1] C. Zachariae,[1,2]
N. Sørensen,[3] O. Pedersen,[4] L. Skov[1,2]
[1]Department of Dermatology and Allergy, Herlev and Gentofte Hospital, University of Copenhagen, Hellerup, Denmark, [2]Copenhagen Research Group for Inflammatory Skin (CORGIS), Hellerup, Denmark, [3]Clinical Microbiomics, Copenhagen, Denmark, [4]Novo Nordisk Foundation Centre for Basic Metabolic Research, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark
*Correspondence. T. Todberg. **E-mail:** tanja.todberg@regionh.dk

References

1 Todberg T, Kaiser H, Zachariae C *et al*. Characterization of oral and gut microbiota in patients with psoriatic diseases: a systematic review. *Acta Derm Venereol* 2021; **101**: adv00512.

2 Valentini V, Silvestri V, Marraffa F *et al*. Gut microbiome profile in psoriatic patients treated and untreated with biologic therapy. *J Dermatol* 2021; **48**: 786–793.

3 Forslund K, Hildebrand F, Nielsen T *et al*. Disentangling type 2 diabetes and metformin treatment signatures in the human gut microbiota. *Nature* 2015; **528**: 262–266.

4 Bryrup T, Thomsen CW, Kern T *et al*. Metformin-induced changes of the gut microbiota in healthy young men: results of a non-blinded, one-armed intervention study. *Diabetologia* 2019; **62**: 1024–1035.

5 Yeh NL, Hsu CY, Tsai TF *et al*. Gut microbiome in psoriasis is perturbed differently during secukinumab and ustekinumab therapy and associated with response to treatment. *Clin Drug Invest* 2019; **39**: 1195–1203.

6 Manasson J, Wallach DS, Guggino G *et al*. IL-17 inhibition in spondyloarthritis associates with subclinical gut microbiome perturbations and a distinctive IL-25-driven intestinal inflammation. *Arthritis Rheumatol* 2019; **72**: 645–657.

DOI: 10.1111/jdv.17952

Burden of treatment in adult patients with atopic dermatitis

Editor,

Atopic dermatitis (AD) carries a substantial disease burden and has a profound impact on quality of life.[1,2] Despite extensive research investigating burden of disease in AD, there is a paucity of research on burden of treatment (BOT) in AD. BOT is the workload of healthcare for patients with chronic conditions and the effects of this on well-being.[3] BOT can affect quality of life as severely as the illness itself.[4] Excessive BOT can lead to negative outcomes such as reduced quality-of-life, non-adherence and wasted resources.[5,6]

This single-centre study aimed to quantify the BOT in adult patients with AD. Data were collected prospectively over a 6-month period. Data on age, gender, AD severity, co-morbidities and prescribed AD treatments were recorded (Table 1). AD severity was graded using the Validated Investigator Global Assessment for AD.[7] The participants completed the anonymous Treatment Burden Questionnaire (TBQ), modified for use in AD for the purpose of this study. TBQ is a validated questionnaire that was developed to quantify BOT in chronic conditions.[8] TBQ incorporates questions on treatment, self-monitoring, follow-up, administrative burden, financial burden and relationship with healthcare providers. Total TBQ scores range from 0 to 150. Patients can be divided into three groups based on their total TBQ score; low, moderate and high treatment burden.[9] It has been demonstrated that patients with a TBQ score of greater than or equal to 59 are at risk of becoming overwhelmed by their treatment, and developing treatment-related burnout.[10]

Ninety-five patients were included in this study; 57% were male, 43% female. Mean age was 38.8 years (median 36, range 18–75). Mean duration since diagnosis of AD was 21.9 years (median 21, range 1–62). 11.6% of patients had mild AD, 41% moderate AD and 47.4% severe AD. 92.6% of patients were using TCS either as monotherapy (48.4%) or in addition to being treated with phototherapy ($n = 9\%$) or systemic therapy. 44.2% of patients were prescribed systemic therapy, predominantly conventional agents (methotrexate, ciclosporin or azathioprine). Prior to May 2021, dupilumab was only available in a very limited capacity through a managed access programme in Ireland, hence the small number of patients treated with dupilumab. AD was associated with a significant BOT in this study, comparable to other chronic diseases, such as Diabetes.[9] Twenty-two percent of patients in this study experienced low BOT, 38.9% moderate BOT and 38.9% high BOT. The mean global BOT score was 55.9/150 indicating a moderate BOT overall among our patient cohort. Almost half (49.4%) of patients had a BOT score of 59 or higher, indicating that the time and effort they are putting into the care of their AD is not sustainable in the long term and that they are at risk of treatment-related burnout.[10] Table 2 depicts the global BOT score stratified by treatment type, and demonstrates a significant BOT across a broad range of treatment options. High BOT in our cohort

Table 1 Patient demographics and disease characteristics

Characteristic	Results
Age – mean (SD)	38.8 (16.6)
Sex – male – *n* (%)	54 (57)
Duration since diagnosis, years [median (IQR)]	21 (7, 30)
Atopic co-morbidities – *n* (%)	
Asthma	41 (43.2)
Allergic rhinitis	11 (11.6)
Food allergy	2 (2.1)
Allergic conjunctivitis	2 (2.1)
Disease severity – *n* (%)	
Mild (IGA 1/2)	11 (12)
Moderate (IGA 3)	39 (41)
Severe (IGA 4)	45 (47)
Prescribed treatment – *n* (%)	
TCS	88 (92.6)
TCS monotherapy	46 (48.4)
Phototherapy	9 (9.5)
Methotrexate	24 (25.3)
Ciclosporin	3 (3.2)
Tofacitinib	6 (6.3)
Mycophenolate mofetil	3 (3.2)
Azathioprine	1 (1.1)
Dupilumab	3 (3.2)

Table 2 Mean global burden of treatment (BOT) stratified by treatment modality

Treatment	Mean global BOT (/150) no. (±SD)
Mycophenolate mofetil	67 (±9.9)
Phototherapy	61.3 (±32.7)
Methotrexate	60.7 (±32.1)
TCS	56.3 (±28.1)
TCS monotherapy	54.2 (±24.7)
Azathioprine	45
Ciclosporin	40 (±35.4)
Tofacitinib	19 (±20.9)
Dupilumab	8 (±3.6)