

Correspondence

Anti-*Saccharomyces cerevisiae* antibodies in hidradenitis suppurativa: More than a gut feeling

To the Editor:

Anti-*Saccharomyces cerevisiae* antibodies (ASCAs) are pANCA antibodies against the mannose portion (mannans) of the fungal cell wall.¹ They have a high sensitivity and specificity as a diagnostic biomarker for Crohn disease and as Assan et al¹ report are associated with severe disease activity in hidradenitis suppurativa (HS). HS is a chronic, inflammatory dermatoses manifesting in painful nodules and abscesses in intertriginous areas often with development of purulent chronically draining epithelialized dermal tunnels.² Clinical outcome measures of disease activity and/or response to pharmacological intervention suffer from poor reproducibility and high placebo response rates.² The identification of ASCAs as a potential diagnostic and disease activity biomarker is an encouraging result in HS, a disease in which biomarkers are sorely needed. However, a critical assessment of the validity of ASCAs in HS and identification of the potential confounding factors that may influence results is mandatory before the consideration of longitudinal, treatment-oriented biomarker validation studies.

HS and Crohn disease have a known epidemiological association¹ and share a number of common inflammatory pathways.¹ The association of ASCAs in HS may be a product of the well-documented overlap in recruitment signaling between skin-homing and gut-homing lymphocytes and antibody-secreting cells in the setting of immune dysregulation such as Crohn disease.³ The comparator population used by Assan et al¹ (psoriasis vulgaris) also has a comparable epidemiological association with Crohn disease,⁴ supporting the validity of their conclusions of increased prevalence of ASCAs in severe HS.¹

The limitations to the study include the exclusion of patients with HS with inflammatory bowel disease or spondyloarthritis, limiting the external validity of ASCAs as a potential biomarker as well as the moderate length of patient follow-up (17 months).¹ Longer follow-up may identify a subset of participants with emergence of Crohn disease. In addition, subclinical Crohn disease may exist in HS participants (as seen in spondyloarthritis),⁵ which would require histological investigation in future replication studies.

An additional consideration in ASCAs as a potential HS biomarker is the significant cross-reactivity with fungal, bacterial,

and mycobacterial species.^{6,7} Various *Candida* species cross-react with ASCAs via surface mannans, and an increase in gastrointestinal candida species results in ASCA titer elevation in murine models.⁶ *Porphyromonas* species (associated with complement activation and clinical disease activity in HS) use oligomannosidases (producing mannans) as virulence factors.⁷ Emerging therapies for HS involve IL-17 blockade, which is known to increase the risk of cutaneous fungal infections. Therefore, although Assan et al's work is an important first step in identifying potential biomarkers in HS, the effect of microbial (bacterial and fungal) colonization and IL-17-based therapy on ASCAs is an important area of future mechanistic and translational enquiry.

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REFERENCES

1. Assan F, Gottlieb J, Tubach F, Lebbah S, Guigue N, Hickman G, et al. Anti-*Saccharomyces cerevisiae* immunoglobulin G and immunoglobulin A antibodies are associated with systemic inflammation and advanced disease in hidradenitis suppurativa [published online ahead of print February 13, 2020]. *J Allergy Clin Immunol*. <https://doi.org/10.1016/j.jaci.2020.01.045>.
2. Frew JW, Jiang CS, Singh N, Grand D, Navrazhina K, Vaughan R, et al. Clinical response rates, placebo response rates, and significant covariates are dependent upon choice of outcome measurement in hidradenitis suppurativa: a post-hoc analysis of PIONEER 1 and 2 individual patient data [published online ahead of print December 24, 2019]. *J Am Acad Dermatol*. <https://doi.org/10.1016/j.jaad.2019.12.044>.
3. Mann ER, McCarthy NE, Peake ST, Milestone AN, Al-Hassi HO, Bernardo D, et al. Skin- and gut-homing molecules on human circulating $\gamma\delta$ T cells and their dysregulation in inflammatory bowel disease. *Clin Exp Immunol* 2012;170:122-30.
4. Alinaghi F, Tekin HG, Burisch J, Wu JJ, Thyssen JP, Egeberg A. Global prevalence and bidirectional association between psoriasis and inflammatory bowel disease—a systematic review and meta-analysis. *J Crohns Colitis* 2020;14:351-60.
5. Rizzo A, Guggino G, Ferrante A, Ciccio F. Role of subclinical gut inflammation in the pathogenesis of spondyloarthritis. *Front Med* 2018;5:63.
6. Schaffer T, Muller S, Flogerzi B, Seibold-Schmid B, Schoepfer AM, Seibold F. Anti-*Saccharomyces cerevisiae* mannan antibodies (ASCA) of Crohn's patients crossreact with mannan from other yeast strains, and murine ASCA IgM can be experimentally induced with *Candida albicans*. *Inflamm Bowel Dis* 2007;13:1339-46.
7. Rangarajan M, Aduse-Opoku J, Hashim A, Paramonov N, Curtis MA. Characterization of the α - and β -mannosidases of *Porphyromonas gingivalis*. *J Bacteriol* 2013;195:5297-307.

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