Eligibility Criteria Related to Hormone Therapy in Acne Clinical Trials: A Systematic Review


TO THE EDITOR

Hormones play a complex role in acne pathogenesis and treatment. Androgens typically increase the size and secretion of sebaceous glands, worsening acne, whereas estrogen counters androgen effect by direct local opposition, inhibition of androgen production, and gene regulation (Barros and Thiboutot, 2017; Beinenfeld et al., 2019). Despite multiple guidelines on acne management, there is a paucity of high-quality data on the treatment of acne among patients receiving hormone therapy (Beinenfeld et al., 2019; Del Rosso et al., 2015; Zaenglein et al., 2016). In the United States, this potentially impacted the treatment of acne among at least 9.1 million women using oral contraceptive pills in 2015–2017 and 2.3 million cisgender and transgender men receiving testosterone replacement therapy (Daniels and Abma, 2018; U.S. Food and Drug Administration, 2018). We sought to examine the inclusion and exclusion criteria of acne clinical trials to identify potential barriers to the enrollment of patients receiving hormone therapy.

We queried ClinicalTrials.gov for interventional studies from 1 January 2009 to 16 May 2019 using the search term acne. All age groups and sexes were included, including those with healthy volunteers. The inclusion and exclusion criteria of acne interventions with a focus on those related to hormone therapy and contraception were analyzed.

Of 121 studies identified, 86 were included (2 duplicates, 8 not related to acne, 25 targeted acne scar appearance) (Table 1). A total of 33 studies (38%) had exclusion criteria related to hormone therapy, including recent changes in therapies such as oral contraceptives, estrogens, and antiandrogenic medications within specified time ranges (ranging from 4 weeks to 1 year). Patients with hormone disorders were excluded in four studies (4.7%). Other exclusion criteria included current use of oral contraceptives (3.5%), androgen blockers (4.7%), and hormone replacement therapy (2.3%). Overall, patients receiving consistent oral contraceptives, androgen blocker therapy, or hormone replacement therapy would be excluded from nine trials (10.5%). Contraceptive requirements were specified in 36 studies (41.9%), which were listed based on gender, sexual behavior, and/or reproductive potential.

Nearly half of acne clinical trials had exclusion criteria that presented potential barriers to patients receiving hormone therapy, including women receiving hormone contraception and men receiving testosterone replacement therapy. In general, women over the age of 25 years with acne tend to have acne that is refractory to conventional therapies and related to androgen production regardless of whether they have clinical signs of hyperandrogenism (Barros and Thiboutot, 2017; Beinenfeld et al., 2019; Del Rosso et al., 2015). Men may experience increased sebum production and acne from testosterone replacement for hypogonadism or gender-affirming hormone therapy, and hormone-related exclusion criteria further contribute to the dearth of evidence on optimizing testosterone-related acne treatment for cisgender and transgender men (Yeung et al., 2019). In some cases, the practice of excluding patients on hormone therapy may be reasonable; clinical trials typically restrict patients newly placed on hormone...
therapy as it may worsen or improve acne, confounding research findings. However, the specific time ranges surrounding changes in hormone therapy are variable between studies and not evidence-based.

Restricting enrollment of patients on hormone therapy or those with hormone-related acne could be moderated by developing clinical trials focused on the treatment of hormone-related acne. However, in our search, only three studies targeted populations with hormone-related acne, and one other study sought general effects of diet on hormonal markers. Our study was limited to clinical trials for acne registered on ClinicalTrials.gov; we did not examine interventions for hyperandrogenism that did not prespecify acne as an outcome.

Acne is the most common dermatologic condition in the United States, yet robust evidence guiding the optimal treatment of acne across diverse patient populations receiving hormone therapy remains scarce. Current guidelines on acne management may apply to women on stable hormone contraception without hormone-related acne. Although one presumes that many acne trials included patients receiving stable hormone therapy, clearly reported data on the inclusion of those receiving hormone therapy are lacking. This may be mitigated by the disaggregation of data by hormone therapy status in future acne clinical trials to demonstrate generalizability to patients receiving stable hormone contraception. Furthermore, the inclusion of diverse populations may not be practical in explanatory clinical trials. Nevertheless, it is important to further demonstrate acne treatment effectiveness across diverse patient populations receiving hormone therapy through pragmatic trials with broadened eligibility criteria or real-world prospective observational studies.

Data availability statement

Datasets related to this article are publicly available at ClinicalTrials.gov.

ORCIDs

Taryn M. DeGrazia: http://orcid.org/0000-0002-1537-3374
Robin Rolader: http://orcid.org/0000-0001-5100-5387
Diane M. Thiboutot: http://orcid.org/0000-0002-7342-2357
Howa Yeung: http://orcid.org/0000-0002-4815-4936

CONFLICT OF INTEREST

HY has received honorarium from Syneos Health. The remaining authors state no conflict of interest.

ACKNOWLEDGMENTS

This study was in part supported by NIAMS L30 AR076081 (HY). We thank Suephy C. Chen for manuscript feedback. Emory University Institutional Review Board determined that this study does not constitute human subjects research, and Institutional Review Board oversight is not required.

AUTHOR CONTRIBUTIONS

Conceptualization: TMD, RR, DMT, HY; Data Curation: TMD, RR, DMT, HY; Formal Analysis: TMD, RR, DMT, HY; Funding Acquisition: TMD, RR, DMT, HY; Methodology: TMD; Project Administration: TMD, RR; Resources: TMD, RR; Software: TMD, RR; Supervision: HY, DMT; Validation: HY; Writing - Original Draft Preparation: TMD; Writing – Review and Editing: TMD, RR, DMT, HY

Taryn M. DeGrazia1*, Robin Rolader1, Diane M. Thiboutot2 and Howa Yeung1,3,*

1Department of Dermatology, Emory University School of Medicine, Atlanta, Georgia, USA; 2Department of Dermatology, Penn State Hershey Dermatology, Hershey, Pennsylvania, USA; and 3Division of Dermatology, Atlanta Regional Telehealth Services, VISN7, Decatur, Georgia, USA

*Corresponding author e-mail: howa.yeung@emory.edu

REFERENCES

Beinenfeld A, Azarchi S, Lo Sicco K, Marchbein S, Shapiro J, Nagler AR. Androgens in women:
Atopic Dermatitis Is Associated with Dermatitis Herpetiformis and Celiac Disease in Children


TO THE EDITOR

Atopic dermatitis (AD) is an eczematous inflammatory skin disease that confers an increased risk for several atopic, somatic, and psychiatric comorbidities (Brunner et al., 2017; Kauppi et al., 2019). Recent epidemiologic data suggest that patients with AD are at risk for several autoimmune diseases (Narla and Silverberg, 2019). Celiac disease (CD) is an autoimmune disease in which dietary gluten intake induces enteropathy (Collin et al., 2017). Dermatitis herpetiformis (DH) is an extraintestinal manifestation of CD presenting with intensely pruritic vesicles on specific skin areas (Collin et al., 2017). Studies analyzing the risk of CD in children and adolescents with AD have found contradictory results (Narla and Silverberg, 2019; Ress et al., 2014). Because the highest reported national prevalence of DH was from a study conducted in Finland (Salmi et al., 2011), we designed the present retrospective nationwide hospital register-based study to examine the risks for CD and DH in children and adolescents with AD.

Study and control populations (Table 1), databases used, and statistical analyses are presented in the Supplementary Materials and Methods online. We found significant association between AD and DH (OR = 10.42, 95% confidence interval [CI] = 6.56–16.55) as well as between AD and CD (OR = 2.28, 95% CI = 2.07–2.52) in pediatric AD population compared with control individuals. After adjusting for healthcare utilization, the associations remained similar (Table 2). Despite the high ORs found for the associations presented, it is important to take into account the rarity of DH and CD when interpreting the results because the prevalence difference of DH between the AD and the control population is 0.099% (95% CI = 0.073–0.124). In a small Estonian study of 351 pediatric patients with AD, the risk of CD was four times greater than in the general pediatric population (OR = 4.18, 95% CI = 1.12–15.64) (Ress et al., 2014). In contrast, in a large cohort study of 9,290 adult and 10,196 pediatric patients with AD in the United States, the risk of CD in children and adolescents with AD was not statistically significant (OR = 2.90, 95% CI = 0.88–9.54) (Narla and Silverberg, 2019). Because DH is relatively rare, a large study population is needed to fully elucidate its association with AD. Moreover, the relatively high prevalence in Finland of both DH and CD (Salmi et al., 2011) may have impacted our findings. The associations between AD and DH and between AD and CD stratified by sex are shown in Supplementary Tables S1 and S2. We found a similar association between AD and both DH and CD in both sexes among the patients with AD. The mean age at AD diagnosis was 6.3 years in patients with AD and 6.8 years versus 5.8 years in girls versus boys, respectively. No statistically significant difference was seen in age at the onset of DH or CD between the AD and the control groups (Supplementary Table S3).

The pathogenesis of DH begins in the gut where ingested gluten induces immune-mediated enteropathy in genetically susceptible individuals, but it is still unclear why only a small proportion of the population develops DH (Reunala et al., 2018). CD is usually latent and asymptomatic in patients with DH (Collin et al., 2017), which leads to prolonged inflammation in the gut. This may over time lead to the production of antibodies against transglutaminase (TG3) through epitope spreading and cross-reactivity between tissue TG2 and TG3 (Kärpätä et al., 2018). It is suggested that TG3 autoimmunity in DH leads to the formation of circulating IgA–TG3 immunocomplexes that deposit in the dermis (Kärpätä et al., 2018). Scratching of itchy AD lesions leads to tissue injury, which results in the release of intracellular autoantigens and thus, activation of immune mechanisms against autoantigens (Tang et al., 2012). Considering that our study revealed that patients with AD face a significantly higher risk of DH than that of CD, it is