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Secukinumab lowers expression of *ACE2* in affected skin of patients with psoriasis

To the Editor:

Current guidance recommends that patients with psoriasis who are diagnosed with coronavirus disease 2019 (COVID-19) discontinue biologic therapy until they recover.[1] However, no evidence supports discontinuation of biologic therapy because of potential risk of infection, and whether biologic therapies increase the risk of COVID-19 infection in patients with psoriasis is not clear.[1-4] Data from randomized studies showed that rates of respiratory infections with biologics were comparable to those seen with placebo.[5] Recently, however, Damiani et al reported that patients with psoriasis who were receiving biologic therapy were at higher risk of testing positive for COVID-19 ($P < .0001$).[6] Interestingly, these patients appeared to be protected from requiring intensive care and from death, with rates of both these measures being similar to those seen in the general population.[6]

It was recently demonstrated that angiotensin-converting enzyme 2 (ACE2) is the main receptor used for entry by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)[7]; however, little is known about the impact of biologic therapy on *ACE2* expression in the skin of patients with psoriasis. To better understand this, we explored the effect of secukinumab treatment on levels of *ACE2* mRNA expression in the skin of patients enrolled in the ObePso-S study (ClinicalTrials.gov identifier NCT03055494).[8]

ObePso-S was a randomized (2:1), double-blind, phase 4 trial investigating the effects of secukinumab on the levels of systemic inflammatory markers and the modulation of gene expression in fat, blood, and skin of patients with moderate-to-severe plaque psoriasis. Patients were treated with secukinumab, 300 mg (n = 54), or placebo (n = 28) for 12 weeks (the placebo-controlled period) and then rolled over to the open-label phase, during which they received secukinumab, 300 mg, every 4 weeks through week 52. A control group of healthy volunteers (n = 17) was included. The study was conducted in accordance with the principles of the Declaration of Helsinki, and all patients provided written informed consent. Lesional and nonlesional 6-mm punch skin biopsies were performed at baseline, week 12, and week 52. *ACE2* expression levels were assessed in the lesional and nonlesional biopsy samples by using mRNA quantification at baseline and at week 12 (see the Methods section of this article's Online Repository at www.jacionline.org). RNA expression was analyzed by using a mixed-effects model, with tissue type (lesional vs nonlesional) and time point (baseline vs week 12) as fixed effects and random effect for the patients. Least square means by group and fold change (FC) were also calculated. Hypotheses were tested by using multiple *t* tests for repeated samples. Correlations with clinical and biologic markers were assessed by using the Pearson method. ACE2 protein expression was detected by immunohistochemistry performed on frozen optimal cutting temperature compound–embedded samples (see the Methods section of the Online Repository).

Baseline patient characteristics are shown in Table E1 (in this article's Online Repository at www.jacionline.org). When assessed at baseline, *ACE2* expression in patients with psoriasis was significantly upregulated in lesional skin compared with in nonlesional skin (FC = 2.03; $P < .001$) and the skin of healthy patients (FC = 1.8; $P < .001$); no significant difference in *ACE2* expression was observed between nonlesional skin and the skin of healthy patients (Fig 1, *A*). When assessed by treatment group, *ACE2* expression was significantly upregulated in lesional versus in nonlesional skin of patients in the placebo and secukinumab groups at baseline ($P < .001$) (Fig 1, *A*), which suggested that inflammation could be influencing *ACE2* expression. To further investigate this, we assessed the correlation between *ACE2* and interleukin 17A (*IL-17A*) expression in lesional skin at baseline and found significant correlation between expression of these genes ($r = 0.33$; $P < .005$). Given that detection levels of *IL-17A* expression in skin were low, we also assessed the correlation between *ACE2* and *IL-17C* at baseline. *ACE2* expression significantly correlated with *IL-17C* expression ($r = 0.57$; $P < .001$) (Fig 1, *B*). We then examined the effect of treatment on *ACE2* expression and found that inhibiting IL-17A–mediated inflammation with secukinumab treatment led to a significant downregulation of *ACE2* expression at week 12 (FC = −2.17; $P < .001$) (Fig 1, *A*); no significant downregulation of *ACE2* expression was observed with placebo (Fig 1, *A*). We also examined the correlation between *ACE2* expression and disease severity (using Psoriasis Area Severity Index [PASI] scores). Although *ACE2* expression did not correlate with PASI scores at baseline (Fig 1, *C*), changes from baseline in *ACE2* expression significantly correlated with changes from baseline in PASI scores at week 12 (Fig 1, *D*). These observations were consistent with clinical outcomes in these patients; at week 12, patients treated with secukinumab had substantial decreases in their PASI scores compared with those patients who received placebo (see Table E1).

We then assessed ACE2 protein expression in the skin and found that it was largely restricted to epithelial cells (keratinocytes) and substantially upregulated in the epidermis of psoriasis lesions, especially in basal keratinocytes (Fig 2). Treatment with secukinumab not only reduced overall ACE2 protein expression in lesional epidermis, but also reduced basal layer expression in both lesional and unaffected skin biopsy samples. This reduced expression in unaffected skin might be due to the elevated levels of circulating IL-17 in patients with psoriasis leading to increased ACE2 expression in background skin, thus affecting expression in other types of epithelial cells.

Overall, our analysis showed that IL-17–mediated inflammation in patients with psoriasis is associated with increased *ACE2* expression in skin plaques. Given that IL-17 exerts its proinflammatory effect systemically, it can be hypothesized that the skin may provide a model epithelium for inflammatory responses that can occur in other organs.[9] If IL-17–mediated inflammation increases *ACE2* expression in other epithelia, untreated inflammatory diseases might lead to an increased risk or severity of COVID-19 infection. Importantly, secukinumab treatment lowered *ACE2* expression to levels similar to those seen in nonlesional skin, which could prove to be advantageous in patients

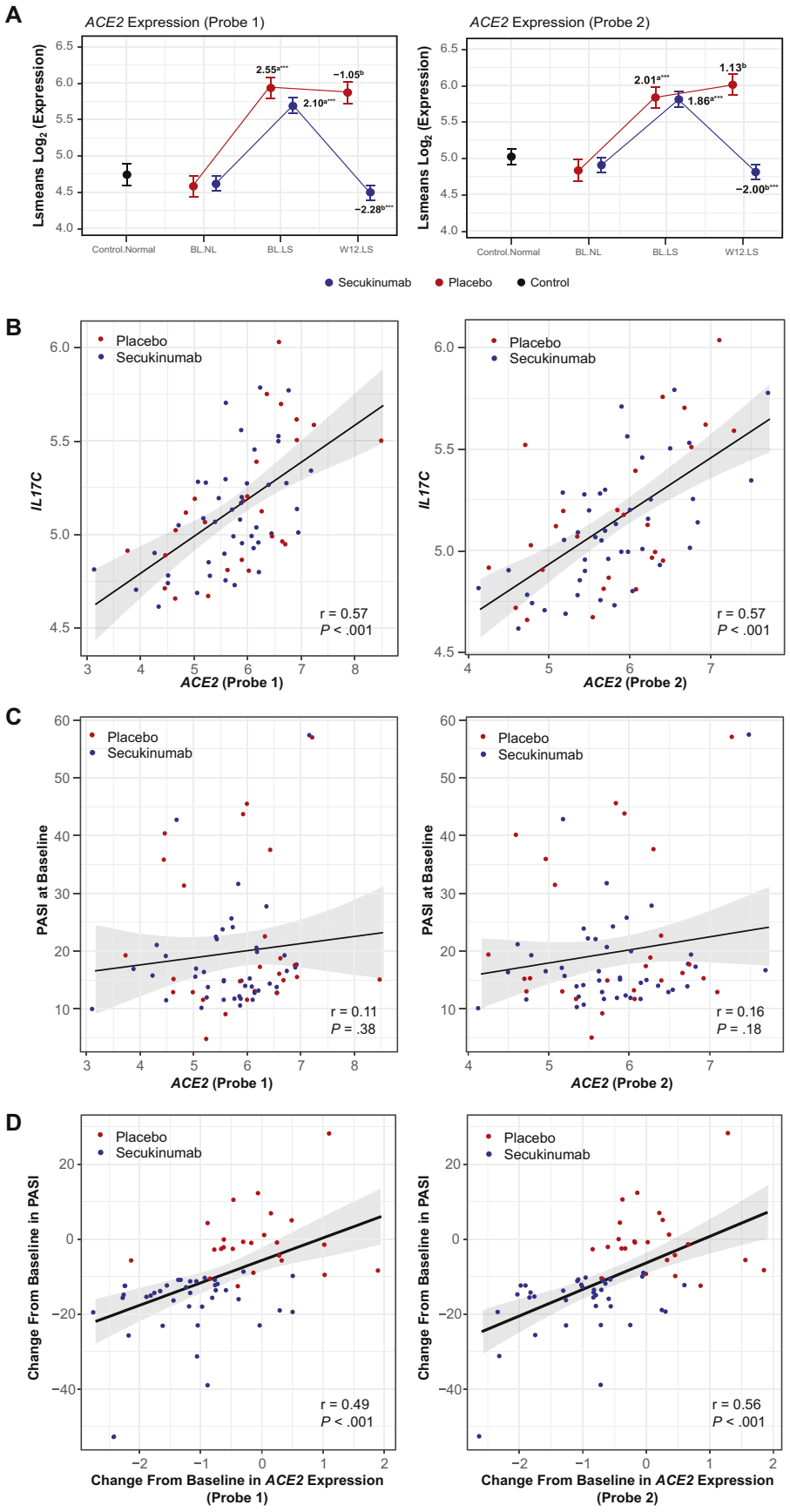

FIG 1. *ACE2* expression in lesional skin of patients with psoriasis treated with secukinumab or placebo. *ACE2* expression at baseline and week 12 by treatment (**A**), correlation between *ACE2* and *IL-17C* expression at baseline (**B**), correlation between Psoriasis Area Severity Index (PASI) scores and *ACE2* expression at baseline (**C**), and correlation between changes in PASI scores and *ACE2* expression at week 12 (**D**). *BL*, Baseline; *LS*, lesional; *LSmeans*, least-squares means; *NL*, nonlesional; *W12*, week 12. *** $P < .001$. [a] Fold change between lesional and nonlesional skin at baseline. [b] Fold change between lesional skin at baseline and lesional skin at week 12.

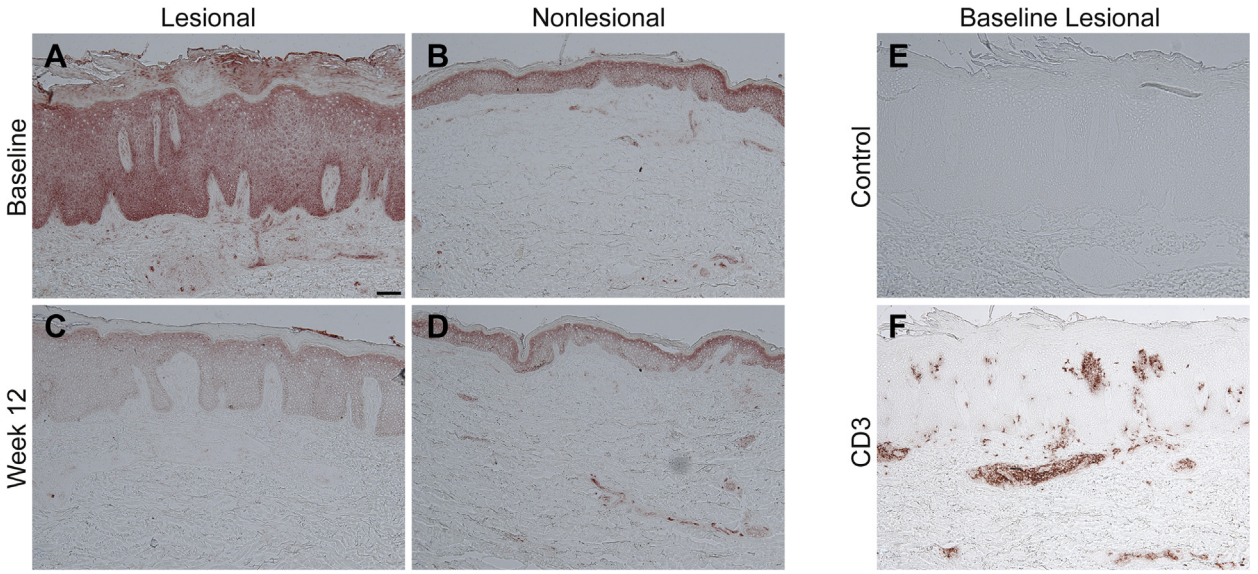

FIG 2. ACE2 staining in lesional and nonlesional skin in patients with psoriasis. **A**, There is a strong upregulation of ACE2 expression in the basal keratinocytes of lesional psoriasis skin. **B**, ACE2 expression is largely restricted to epithelial cells (keratinocytes). **C**, Treatment with secukinumab reduces overall ACE2 protein expression in the lesional epidermis and decreases basal layer expression in both lesional and nonlesional skin (**C** and **D**). **E**, Negative control demonstrates that the secondary antibody does not produce background staining. **F**, CD3 staining of baseline lesional skin is shown to demonstrate that a specific antibody to another target does not stain the epidermis. Scale bar = 100 μm.

with psoriasis who are at risk for SARS-CoV-2 infection; however, additional studies are needed to determine whether similar findings are observed in other organs. Although further studies are warranted, our findings add new information on the relationship between IL-17–related inflammation and expression levels of the SARS-CoV-2 receptor/*ACE2* in peripheral tissues. This information is 1 factor to consider in management of T-cell–mediated inflammatory diseases during the COVID-19 pandemic.

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METHODS

RNA quantification

RNA was extracted, followed by hybridization to Affymetrix Human U133Plus 2.0 gene arrays (Affymetrix, Santa Clara, Calif), as previously described, by using probes 222257_s_at and 219962_at.[E1] Quality control of the microarray chips was carried out with standard quality control metrics and the R software package microarray quality control. Images were scrutinized for spatial artifacts by using Harshlight.[E2] Expression measures were obtained with the GCRMA algorithm.[E3] A batch effect, corresponding to the hybridization date, was detected by using principal component analysis and adjusted with the ComBat function from the R software package sva.

Immunohistochemistry

Immunohistochemistry was performed on frozen optimal cutting temperature compound–embedded samples. Samples were fixed in acetone, blocked in 10% normal serum, incubated overnight in primary antibody at 4°C, washed, blocked in biotinylated secondary antibody at room temperature for 30 minutes (Vector Laboratories, Burlingame, Calif), and developed with the chromogen 3-amino-9-ethylcarbazole (AEC, Sigma-Aldrich, Burlington, Mass). The antibodies used were ACE2 (Sigma-Aldrich, catalog no. HPA000288) and CD3(SK7) (BD Biosciences, San Jose, Calif).

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TABLE E1. Patient characteristics

Demographic characteristic	Patients receiving secukinumab (n = 54)	Patients receiving placebo (n = 28)
Age (y), median (range)	40.5 (18-79)	52.0 (25-70)
Male, n (%)	32 (59.3)	20 (71.4)
BMI (kg/m^2), mean (SD)	31.8 (8.0)	34.9 (12.2)
Time since diagnosis of plaque psoriasis, median, y (range)	10.0 (0-38)	11.0 (0-36)
Psoriatic arthritis, n (%)	10 (18.5)	1 (3.6)
Prior psoriasis therapy, n (%)*		
Biologic systemic therapy	14 (25.9)	5 (17.9)
Nonbiologic systemic therapy	19 (35.2)	12 (42.9)
Topical therapy	47 (87.0)	22 (78.6)
Phototherapy	9 (16.7)	5 (17.9)
Disease activity at baseline		
PASI score, mean (SD)	19.0 (7.3)	22.9 (13.7)
Disease activity at wk 12		
PASI score, mean (SD)	2.0 (2.6)	22.1 (14.1)

BMI, Body mass index; *PASI*, Psoriasis Area and Severity Index.
*Patients may have received 1 or more prior therapies.