CORRESPONDENCE

Inhibition of the Interleukin-36 Pathway for the Treatment of Generalized Pustular Psoriasis

TO THE EDITOR: Generalized pustular psoriasis is a rare, life-threatening disease characterized by recurrent flares of pustular, erythematous rashes.[1] In some patients with this disease, loss-of-function mutations have been found in *IL36RN*, which encodes an interleukin-36–receptor antagonist.[2,3] This finding suggests that the interleukin-36 pathway may be involved in the pathogenesis of this disorder.[4]

We report the results of a phase 1 proof-of-concept study involving seven patients who presented with a generalized pustular psoriasis flare and were treated with a single, open-label, intravenous dose of BI 655130, a monoclonal antibody against the interleukin-36 receptor,[5] at 10 mg per kilogram of body weight (ClinicalTrials.gov number, NCT02978690). (The study protocol is available with the full text of this letter at NEJM.org.)

At baseline, all the patients were evaluated with the use of the Generalized Pustular Psoriasis Physician Global Assessment (GPPGA), a physician-based assessment of the severity of pustules, erythema, and scaling of generalized pustular psoriasis lesions. Each component is scored on a five-point scale, ranging from 0 (least severe) to 4 (most severe), and the average is calculated. (Details about scoring are provided in the Supplementary Appendix, available at NEJM.org.) All the patients had an average GPPGA score of 3 (moderate disease), with a pustule subscore of 2 to 4. Three patients had a homozygous *IL36RN* mutation, one of whom also had a heterozygous mutation in *CARD14* (which has been linked to pustular skin disease), and four did not have any of the target mutations (*IL36RN*, *CARD14*, and *AP1S3*) (Table S1 in the Supplementary Appendix).

After the infusion of the study drug, all the patients had adverse events that were graded as mild or moderate, and no serious adverse events were reported (Table S2 in the Supplementary Appendix). A GPPGA score of 0 or 1 (clear or almost clear skin) was achieved in five patients by week 1 and in all patients (with or without the *IL36RN* mutation) by week 4 (Fig. 1A and 1B). The patients were also evaluated with the use of the Generalized Pustular Psoriasis Area and Severity Index (GPPASI), an adaptation of the PASI score in which the induration component is replaced by a pustule component, with a total score ranging from 0 (least severe) to 72 (most severe) (see the Supplementary Appendix). Among the study patients, the mean percent improvement in the GPPASI score from baseline was 59.0% at week 1, 73.2% at week 2, and 79.8% at week 4 (Fig. 1C). Pustules were completely cleared in three patients within 48 hours after treatment, in five patients by week 1, and in six patients by week 2 (Fig. S1 in the Supplementary Appendix). GPPGA, GPPASI, and pustule subscores were maintained up to week 20. A reduction in the mean (±SD) level of C-reactive protein that approached normalization was observed from baseline to week 2 (from 69.4±57.0 mg per deciliter to 4.5±7.5 mg per deciliter) and was

THIS WEEK'S LETTERS

981 Inhibition of the Interleukin-36 Pathway for the Treatment of Generalized Pustular Psoriasis

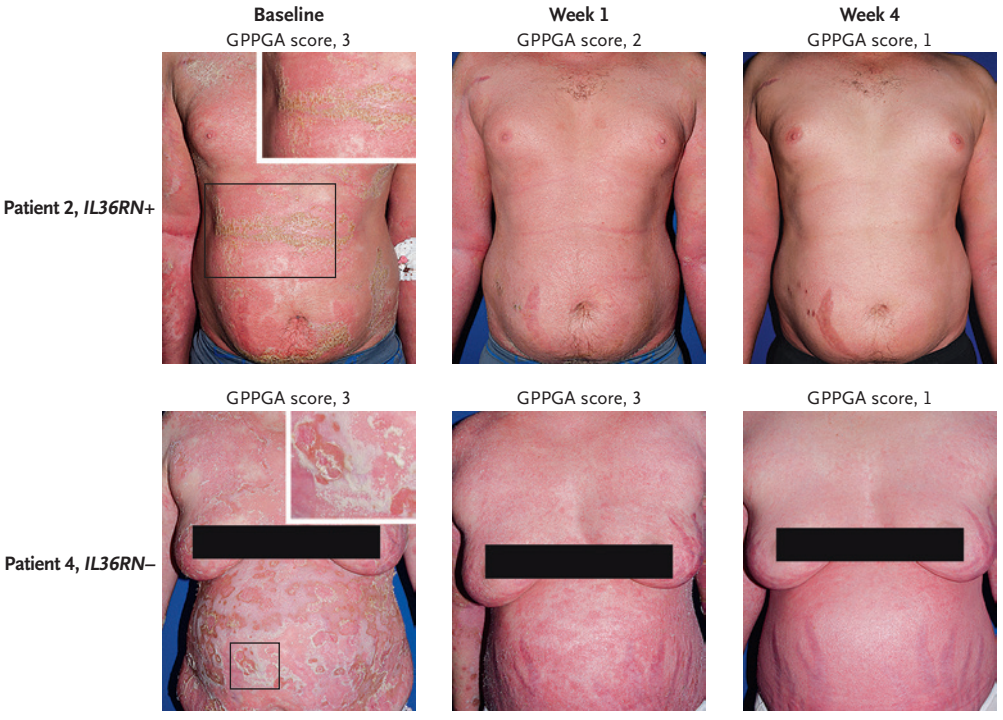
983 Pantoprazole in Patients in the ICU

985 Atezolizumab and Nab-Paclitaxel in Advanced Triple-Negative Breast Cancer

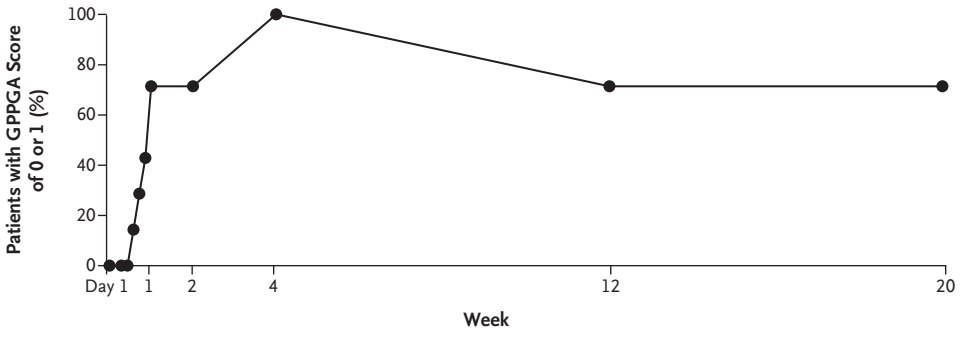
988 Rivaroxaban in Patients with Heart Failure

989 Durvalumab after Chemoradiotherapy in Stage III Non–Small-Cell Lung Cancer

A Two Study Patients before and after Treatment with BI 655130



B GPPGA Score of 0 or 1



C Change in GPPASI after Treatment

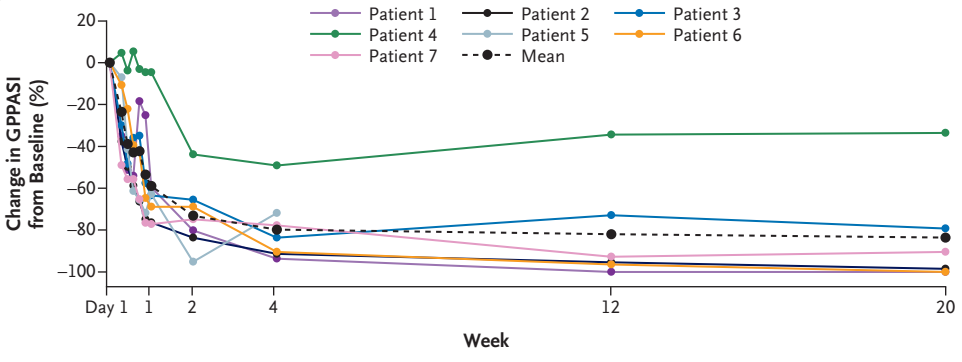


Figure 1 (facing page). Response to Treatment among the Seven Study Patients.

Panel A shows photographs of two patients with generalized pustular psoriasis, one of whom had the *IL36RN* mutation (upper row) and one of whom did not have the mutation (bottom row). The images were taken at baseline (before treatment) and at week 1 and week 4 after treatment with a single intravenous dose of BI 655130. Panel B shows the percentage of the seven study patients who had a score of 0 (clear) or 1 (almost clear) on the Generalized Pustular Psoriasis Physician Global Assessment (GPPGA) through week 20. Of the three patients with an *IL36RN* mutation, a GPPGA score of 0 or 1 was reported in two patients by week 1 and in all three patients by week 4. At week 2, a GPPGA score for one patient was missing. Panel C shows the percent change from baseline in the Generalized Pustular Psoriasis Area and Severity Index (GPPASI) for each patient; patients 1, 2, and 7 were positive for the *IL36RN* mutation. One patient (Patient 5) received methotrexate after week 4 for the treatment of pain, so data for this patient were censored at weeks 12 and 20.

sustained until the last measurement was obtained at week 4 (Fig. S2 in the Supplementary Appendix).

The efficacy of BI 655130 regardless of the presence of the *IL36RN* mutation suggests that the interleukin-36 pathway may play a pathogenic role among patients with generalized pustular psoriasis who have different genetic backgrounds, including those without target mutations. This proof-of-concept study suggests that the inhibition of interleukin-36 receptor with a single dose of BI 655130 may reduce the severity of generalized pustular psoriasis over a 20-week period, as was observed in our patients. However, further clinical investigation is required to determine the clinical efficacy, duration of effect, and adverse events associated with the drug.

Hervé Bachelez, M.D., Ph.D.
Sorbonne Paris Cité Université Paris Diderot
Paris, France
herve.bachelez@aphp.fr

Siew-Eng Choon, F.R.C.P.
Monash University Malaysia
Johor Bahru, Malaysia

Slaheddine Marrakchi, M.D.
Hedi Chaker University Hospital
Sfax, Tunisia

A. David Burden, M.D.
University of Glasgow
Glasgow, United Kingdom

Tsen-Fang Tsai, M.D.
National Taiwan University
Taipei, Taiwan

Akimichi Morita, M.D.
Nagoya City University
Nagoya, Japan

Hamida Turki, M.D.
Hedi Chaker University Hospital
Sfax, Tunisia

David B. Hall, Ph.D.
Boehringer Ingelheim Pharmaceuticals
Ridgefield, CT

Michael Shear, M.Sc.
Patrick Baum, Ph.D.
Boehringer Ingelheim International
Biberach, Germany

Steven J. Padula, M.D.
Boehringer Ingelheim International
Ingelheim, Germany

Christian Thoma, M.D.
Boehringer Ingelheim International
Biberach, Germany

Supported by Boehringer Ingelheim.

Disclosure forms provided by the authors are available with the full text of this letter at NEJM.org.

1. Navarini AA, Burden AD, Capon F, et al. European consensus statement on phenotypes of pustular psoriasis. J Eur Acad Dermatol Venereol 2017;31:1792-9.
2. Marrakchi S, Guigue P, Renshaw BR, et al. Interleukin-36–receptor antagonist deficiency and generalized pustular psoriasis. N Engl J Med 2011;365:620-8.
3. Onoufriadis A, Simpson MA, Pink AE, et al. Mutations in IL36RN/IL1F5 are associated with the severe episodic inflammatory skin disease known as generalized pustular psoriasis. Am J Hum Genet 2011;89:432-7.
4. Johnston A, Xing X, Wolterink L, et al. IL-1 and IL-36 are dominant cytokines in generalized pustular psoriasis. J Allergy Clin Immunol 2017;140:109-20.
5. Ganesan R, Raymond EL, Mennerich D, et al. Generation and functional characterization of anti-human and anti-mouse IL-36R antagonist monoclonal antibodies. MAbs 2017;9:1143-54.

DOI: 10.1056/NEJMc1811317

Pantoprazole in Patients in the ICU

TO THE EDITOR: The trial conducted by Krag et al. (Dec. 6 issue)[1] showed no significant difference in 90-day mortality between the pantoprazole group and the placebo group among patients in the intensive care unit (ICU) who were at risk for gastrointestinal hemorrhage. However, the trial