ic and clinical burden of nonalcoholic steatohepatitis (NASH) in the United States. J Clin Exp Hepatol 2023;13:454-67.
13. Lomonaco R, Godinez Leiva E, Bril F, et al. Advanced liver fibrosis is common in patients with type 2 diabetes followed in the outpatient setting: the need for systematic screening. Diabetes Care 2021;44:399-406.
14. Ajmera V, Cepin S, Tesfai K, et al. A prospective study on the prevalence of NAFLD, advanced fibrosis, cirrhosis and hepatocellular carcinoma in people with type 2 diabetes. J Hepatol 2023;78:471-8.
DOI: 10.1056/NEJMe2314365

Psoriasis — More Progress but More Questions

Joel M. Gelfand, M.D., M.S.C.E.

Psoriasis is a chronic inflammatory disease that affects more than 60 million persons worldwide and is characterized by red, scaly plaques that itch, crack, and bleed. Any area of the skin can be affected, with the scalp, genitals, palms, and soles being especially burdensome. The disease course is varied; approximately 20% of patients have moderate-to-severe cutaneous involvement, and among those patients, inflammatory arthritis develops in approximately 30%. Advances in genetics, immunology, and epidemiology have redefined psoriasis — previously thought to be "just a skin disease" — as a systemic condition associated with obesity, diabetes, major cardiovascular events, and a life expectancy of 5 years less than that of persons without psoriasis.[1-3]

Although psoriasis is multisystemic, clinical trials have focused on the skin response. The most common physician-reported end point is the Psoriasis Area and Severity Index (PASI). This index accounts for the degree of red, scaly, and thick plaques and multiplies this factor by the area of affected skin, yielding scores that range from 0 to 72, with higher scores indicating greater extent or severity of psoriasis. Traditionally, a 75% reduction in the PASI score (i.e., PASI 75 response) has been chosen to be the primary end point. A 90% reduction in the PASI score (i.e., PASI 90 response) is similar to a result of clear or nearly clear skin, indicates a better clinical response than the PASI 75 response, and is increasingly the standard by which therapeutic agents for psoriasis are judged.

Over the past two decades, stunning progress has been made in the treatment of moderate-to-severe psoriasis. Most of these advances have been the development of monoclonal antibodies — large proteins that are administered parenterally. In the early 2000s, subcutaneous tumor necrosis factor α (TNF-α) inhibitors such as etanercept and adalimumab resulted in a PASI 90 response in 20 to 45% of patients.[4] Subsequently, ustekinumab (which targets interleukin-12 and interleukin-23) was associated with a PASI 90 response in 45% of patients.[4] In the 2010s, biologic agents targeting interleukin-17A (brodalumab, ixekizumab, and secukinumab) and interleukin-23 (guselkumab, risankizumab, and tildrakizumab) led to PASI 90 responses in 56 to 70% and in 36 to 75% of patients, respectively. More recently, bimekizumab, which targets interleukin-17A and interleukin-17F, was associated with a PASI 90 response in 86%.[5]

In this issue of the *Journal*, Bissonnette et al.[6] report the results of a phase 2 dose-finding trial of an orally administered interleukin-23–receptor antagonist peptide (JNJ-77242113) that blocks interleukin-23 signaling and the resulting interleukin-17 production. Advances in bioengineering have made it possible for complex proteins to penetrate gastrointestinal proteases, mucus, and cellular barriers, thereby enabling oral bioavailability; semaglutide is a notable example.[7]

JNJ-77242113 showed a dose–response relationship, with the highest dose (100 mg twice daily) resulting in a PASI 90 response in 60% of patients, which — if confirmed by larger studies — would be similar to the most effective injectable biologics.[4] Moreover, there was no evidence of a relationship between the JNJ-77242113 dose and the occurrence of side effects. However, two occurrences of infection (coronavirus disease 2019 and an infected cyst) and a suicide attempt were reported as serious adverse events; larger trials will be needed to determine whether such events are attributable to chance, psoriasis itself, or inhibition of interleukin-23 signaling. Furthermore, JNJ-77242113 needs to be taken on an empty stomach, and therefore, effectiveness may be lower in real-world settings. The response may also be di-

minished by obesity. For example, in the highest dose group, 100% of the patients with a body-mass index (BMI; the weight in kilograms divided by the square of the height in meters) of less than 25 had a PASI 75 response as compared with 68% of those with a BMI of 30 or higher.

The progress made with regard to skin clearance in patients with psoriasis is tempered by the relative lack of progress in understanding the effect of these treatments on preventing the development of psoriatic arthritis, diabetes, cardiovascular disease, and premature death — conditions that substantially affect patients with moderate-to-severe psoriasis. Placebo-controlled trials of adalimumab, ustekinumab, secukinumab, and phototherapy have shown that although these treatments are effective in improving skin signs of psoriasis, their effects on inflammatory cytokines that cause atherosclerosis vary, and they have limited or no effect on aortic vascular inflammation, flow-mediated dilatation, lipid levels, and glucose metabolism.[8] Observational studies suggest that some psoriasis treatments (e.g., TNF-α inhibitors and methotrexate) are associated with a reduction in cardiovascular risk, but these studies are limited by a "healthy user" effect. Moreover, in a large trial involving patients with atherosclerosis, methotrexate therapy notably failed to prevent the occurrence of cardiovascular events.[9] Patients with rheumatoid arthritis who are taking TNF-α inhibitors have a lower risk of cardiovascular events than those taking the Janus kinase inhibitor tofacitinib.[10] However, whether this finding is the result of a reduced risk associated with TNF-α inhibitors or an increased risk associated with Janus kinase inhibitors is unclear.

To further advance the science and clinical management of psoriasis, the next generation of trials will need to have a randomized design, active comparators, larger sample sizes, and longer durations in order to determine which treatment targets, if any, prevent the onset of psoriatic arthritis and cardiometabolic disease. Such effects will restore to normal not only the skin but also the patient's overall health and life span. Only then will the full promise of these advances be realized.

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

From the Departments of Dermatology and Biostatistics, Epidemiology, and Informatics, University of Pennsylvania Perelman School of Medicine, Philadelphia.

1. Gelfand JM, Neimann AL, Shin DB, Wang X, Margolis DJ, Troxel AB. Risk of myocardial infarction in patients with psoriasis. JAMA 2006;296:1735-41.
2. Elmets CA, Leonardi CL, Davis DMR, et al. Joint AAD-NPF guidelines of care for the management and treatment of psoriasis with awareness and attention to comorbidities. J Am Acad Dermatol 2019;80:1073-113.
3. Noe MH, Shin DB, Wan MT, Gelfand JM. Objective measures of psoriasis severity predict mortality: a prospective population-based cohort study. J Invest Dermatol 2018;138:228-30.
4. Sbidian E, Chaimani A, Guelimi R, et al. Systemic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis. Cochrane Database Syst Rev 2023;7:CD011535.
5. Reich K, Warren RB, Lebwohl M, et al. Bimekizumab versus secukinumab in plaque psoriasis. N Engl J Med 2021;385:142-52.
6. Bissonnette R, Pinter A, Ferris LK, et al. An oral interleukin-23–receptor antagonist peptide for plaque psoriasis. N Engl J Med 2024;390:510-21.
7. Drucker DJ. Advances in oral peptide therapeutics. Nat Rev Drug Discov 2020;19:277-89.
8. González-Cantero A, Ortega-Quijano D, Álvarez-Díaz N, et al. Impact of biological agents on imaging and biomarkers of cardiovascular disease in patients with psoriasis: a systematic review and meta-analysis of randomized placebo-controlled trials. J Invest Dermatol 2021;141:2402-11.
9. Ridker PM, Everett BM, Pradhan A, et al. Low-dose methotrexate for the prevention of atherosclerotic events. N Engl J Med 2019;380:752-62.
10. Ytterberg SR, Bhatt DL, Mikuls TR, et al. Cardiovascular and cancer risk with tofacitinib in rheumatoid arthritis. N Engl J Med 2022;386:316-26.

DOI: 10.1056/NEJMe2314345