EDITORIAL

Targeting Cardiometabolic Disease to Improve Psoriasis—A New Treatment Paradigm Emerges

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Imagine a new patient visit with a man aged 45 years who has a 15-year history of psoriasis. On examination, he has a body mass index (calculated as weight in kilograms divided by height in meters squared) of 40, a blood pressure of 144/86 mm/Hg, and well-demarcated red, scaly plaques on the extensor surfaces of the arms, legs, trunk, and scalp, involving 25% of the body surface area. You can select an injectable treatment that has a 30% chance of achieving 100% clear skin or another approach that has a 40% chance of achieving 100% clear skin and also lowers his weight by 15%, triglycerides by 30 mg/dL (to convert to mmol/L, multiply by 0.0113), hemoglobin A_{1c} by 0.6%, and systolic blood pressure by 10 mm Hg. Which would you choose? The choice is no longer theoretical, based on the results of the paradigm-shifting TOGETHER-PsO trial.[1]

Related article

Psoriasis is an obesity-related condition that is recognized by the American College of Cardiology and American Heart Association as a cardiovascular risk enhancer and promoter of hypertriglyceridemia.[2] A breadth of epidemiologic, immunologic, genetic, and imaging data demonstrates patients with psoriasis are up to 2-fold more likely to have obesity and that obesity (1) increases the risk of psoriasis and psoriatic arthritis, (2) is directly associated with more extensive (eg, severe) skin involvement, and (3) reduces response to treatment and increases loss of response to treatment over time.[3] Moreover, patients with psoriasis have increased, metabolically active, visceral adiposity (fat surrounding internal organs), which promotes insulin resistance, dyslipidemia, systemic inflammation, and atherosclerosis.[4] At the population level, obesity is a major driver of poor cardiovascular health in people with psoriasis.[5] Despite the effectiveness of current psoriasis treatments, none are demonstrated to improve cardiometabolic disease or reduce cardiovascular risk.[6] In contrast, multiple trials indicate that hypocaloric dietary weight loss interventions improve psoriasis but are difficult to maintain.

Incretins are gut-derived hormones, principally glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP), that regulate glucose, digestion, and appetite and result in approximately 15% to 20% body weight loss after a year of therapy.[7] They are approved for treatment of diabetes, obesity, and obesity-associated obstructive sleep apnea and are demonstrated to reduce cardiovascular events and kidney disease while improving metabolic dysfunction-associated steatohepatitis (formerly nonalcoholic steatohepatitis), all of which are psoriasis-associated conditions. GLP-1 receptors are not only present in the pancreas, brain, and gastrointestinal tract but also throughout the cardiovascular system in addition to being overexpressed in psoriasis plaques.[8] Furthermore, GLP-1 receptor agonists modulate key inflammatory pathways (interleukin 17 and tumor necrosis growth factor α) that drive psoriasis activity, and genetic proxies of GLP-1 receptor expression are causally associated with a reduced risk of psoriasis and psoriatic arthritis.[9]

In this context, the TOGETHER-PsO trial[1] investigated the benefit of adding tirzepatide (a GLP-1/GIP agonist) to ixekizumab (a biologic targeting interleukin 17) for the treatment of patients with moderate to severe psoriasis and overweight (with hypertension, dyslipidemia, sleep apnea, cardiovascular disease, or type 2 diabetes) or obesity. Participants were randomly assigned to open-label ixekizumab or ixekizumab plus tirzepatide. There was no placebo control, and skin assessments were conducted by assessors blinded to treatment assignment. At week 36, 27.1% met the primary end point of achieving a Psoriasis Activity and Severity Index (PASI) score of 100 and 10% or more weight loss in the tirzepatide plus ixekizumab group compared with 5.8% in the ixekizumab alone group ($P < .001$). A total of 40.6% of patients receiving ixekizumab plus tirzepatide achieved a PASI score of 100 vs 29.0% in the ixekizumab alone group ($P = .04$). This change was clinically meaningful, with 72% of patients taking tirzepatide plus ixekizumab achieving no impact of psoriasis on skin-related quality of life vs 58% on ixekizumab alone ($P = .02$). The metabolic benefits of the combination were clinically important, including approximately a 30-mg/dL reduction in triglycerides and a 10 mm Hg-reduction in systolic blood pressure, an improvement on par with that observed in antihypertensive clinical trials and shown to reduce cardiovascular events by up to 20%.[10] These findings add to the recent TOGETHER-PsA trial results, which observed greater improvements in American College of Rheumatology response criteria in the ixekizumab plus tirzepatide group (33.5%) vs the ixekizumab alone group (20.4%) ($P = .02$) in adults with active psoriatic arthritis as a secondary end point.[11]

There are, however, important limitations to consider. The study was open label, lacked a placebo, and the estimate of the skin benefits was imprecise and the secondary end point of the trial. Also, the degree to which skin benefits were due to direct anti-inflammatory effects of tirzepatide, weight loss, or changes in pharmacokinetics of ixekizumab associated with weight loss is not known. Double-blind, placebo-controlled randomized trials of monotherapy incretin agonists in patients with psoriasis and overweight or obesity are needed to fully define their skin benefits. For some patients, particularly those with obesity and mild to moderate psoriasis, it is possible that their psoriasis may remit with incretin agonists alone, which

would establish a new paradigm in which a patient with overweight or obesity and psoriasis is first treated with incretin therapy, and if psoriasis does not remit, then skin-targeted treatments can be added as needed. To further expand on this concept, clinical trials are also needed to investigate the impact of standard cardiovascular prevention medications, including statins and proprotein convertase subtilisin/kexin type 9 inhibitors, on the natural history of psoriasis. Statins are particularly promising candidates for disease modification in psoriasis, as they are associated with a reduced risk of psoriatic arthritis in observational studies and reduced Psoriasis Activity and Severity Index scores in small, short-term clinical trials, and recent genetic data suggest atherosclerosis may cause psoriasis.[4] Similarly, mendelian randomization studies suggest a causal role of proprotein convertase subtilisin/kexin type 9 signaling in psoriasis.[4]

Nevertheless, the results of the TOGETHER-PsO trial are a call to action for dermatologists. Cardiovascular disease in patients with psoriasis starts early with endothelial damage (a precursor to clinical atherosclerosis), potentiated by proinflammatory cytokines,[12] dyslipidemia, insulin resistance, and overactivated platelets (thrombo-inflammation).[13] Indeed, psoriasis can be thought of as a skin sign of metabolic syndrome, atherosclerosis, and excess cardiovascular mortality, the risk of which increases with increasing extent of skin involvement. Despite the breadth of evidence linking psoriasis in a dose-response manner with cardiometabolic disease, pervasive and persistent underdiagnosis and undertreatment of cardiovascular risk factors in patients with psoriasis continues to result in preventable morbidity and mortality.[4] Dermatologists should, at a minimum, screen for cardiometabolic disease in patients with moderate to severe psoriasis, including blood pressure, hemoglobin A_{1c}, lipids, and body mass index, and consider calculating a cardiovascular risk score or recommend that the patient undergo these routine tests by their primary clinician or other health care professional.[2,4] Early results of a care coordination model supported by the National Psoriasis Foundation demonstrate the feasibility and clinical benefits of dermatologists screening for cardiovascular risk factors in patients with psoriasis and patients welcome dermatologist screening of cardiovascular risk factors in the context of providing psoriasis care.[14,15] Just as dermatologists collaborate with rheumatologists on psoriatic arthritis, they need to collaborate with primary care clinicians, obesity specialists, endocrinologists, and preventive cardiologists to ensure that their patients not only achieve clear skin but also receive the counseling, nutrition, exercise, and medical therapies needed to improve their overall health and lifespan.

ARTICLE INFORMATION

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REFERENCES

1. Lebwohl M, Blauvelt A, Kartman CE, Leatherwood C, Gordon KB. Ixekizumab with or without tirzepatide in adults with psoriasis and overweight or obesity: the TOGETHER-PsO phase 3b randomized clinical trial. *JAMA Dermatol*. Published online May 15, 2026. doi:10.1001/jamadermatol.2026.1753

2. Blumenthal RS, Morris PB, Gaudino M, et al; Writing Committee Members. 2026 ACC/AHA/AACVPR/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Dyslipidemia: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*. 2026;153(17):e1154-e1276. doi:10.1161/CIR.0000000000001423

3. Gelfand JM. The visceral relationship of psoriasis and obesity. *J Invest Dermatol*. 2025;145(11):2657-2658. doi:10.1016/j.jid.2025.04.013

4. Gelfand JM, Song WB, Langan SM, Garshick MS. Cardiodermatology: the heart of the connection between the skin and cardiovascular disease. *Nat Rev Cardiol*. 2025;22(5):354-371. doi:10.1038/s41569-024-01097-9

5. Wang S, Shin DB, Bhutani T, Garshick MS, Gelfand JM. Cardiovascular health in people with psoriasis: a population-based study in the United States. *J Invest Dermatol*. 2023;143(10):2075-2078. doi:10.1016/j.jid.2023.04.006

6. Gelfand JM. Psoriasis - more progress but more questions. *N Engl J Med*. 2024;390(6):561-562. doi:10.1056/NEJMe2314345

7. Drucker DJ. The expanding landscape of GLP-1 medicines. *Nat Med*. 2026;32(1):47-57. doi:10.1038/s41591-025-04124-5

8. Narla S, Narla RR, Corbett JA. JAAD CME part 1: mechanism of action of GLP-1 receptor agonists and potential pathways in skin health. *J Am Acad Dermatol*. Published online February 16, 2026. doi:10.1016/j.jaad.2026.01.088

9. Ramessur R, Arham AGA, Saklatvala J, et al. Genetic proxies of GLP1R expression are associated with lower risk of psoriasis and psoriatic arthritis. *Br J Dermatol*. Published online April 28, 2026. doi:10.1093/bjd/ljag163

10. Ettehad D, Emdin CA, Kiran A, et al. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. *Lancet*. 2016;387(10022):957-967. doi:10.1016/S0140-6736(15)01225-8

11. Merola JF, Mease P, Kivitz A, et al. Ixekizumab with tirzepatide achieved greater disease control than ixekizumab alone in adults with psoriatic arthritis and overweight or obesity: results from a randomized clinical trial. *Arthritis Rheumatol*. Published online March 28, 2026. doi:10.1002/art.70134

12. Garshick MS, Barrett TJ, Wechter T, et al. Inflammasome signaling and impaired vascular health in psoriasis. *Arterioscler Thromb Vasc Biol*. 2019;39(4):787-798. doi:10.1161/ATVBAHA.118.312246

13. Garshick MS, Drenkova K, Kazatsker F, et al. Platelet activation and a platelet biosignature are associated with cardiovascular risk in patients with controlled psoriasis. *Arterioscler Thromb Vasc Biol*. 2025;45(11):2086-2096. doi:10.1161/ATVBAHA.125.322574

14. Barbieri JS, Beidas RS, Gondo GC, et al. Analysis of specialist and patient perspectives on strategies to improve cardiovascular disease prevention among persons with psoriatic disease. *JAMA Dermatol*. 2022;158(3):252-259. doi:10.1001/jamadermatol.2021.4467

15. Song WB, Garshick MS, Barbieri JS, et al. A care coordination model to prevent cardiovascular events in patients with psoriatic disease: a multicenter pilot study. *J Invest Dermatol*. 2024;144(6):1405-1409.e1. doi:10.1016/j.jid.2023.12.008