Psoriatic arthritis is a chronic seronegative, inflammatory arthropathy with a prevalence that varies from 6% to 39% among patients with psoriasis. Psoriatic arthritis in the United States is estimated to affect 11% of patients with psoriasis.1 Owing to this high prevalence, dermatologists are often confronted with the diagnosis and management of psoriatic joint disease. Although there are a number of treatment options for both conditions, drugs that target tumor necrosis factor (TNF) have become first-line therapy for moderate to severe disease in recent years.2-4

A newer treatment option for plaque psoriasis involves blocking the p40 subunit of interleukin (IL) 12 and IL-23. The pathogenesis of psoriasis has been linked to an aberrant type 1 immune response that leads to increased cytokine expression, specifically IL-12 and IL-23.5,6 These interleukins activate T cells expressing IL-17, a cytokine that plays an important role in the pathogenesis of joint destruction associated with psoriatic arthritis.7,8

Ustekinumab is a human monoclonal antibody that binds to the shared p40 subunit of interleukin (IL) 12 and IL-23. It is approved in the United States for adults (>18 years) with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy. In 1 phase 2 trial of ustekinumab for treatment of psoriatic arthritis, joint disease improved.

We describe 4 patients receiving ustekinumab monotherapy for plaque psoriasis who developed disabling flares of known psoriatic arthritis or unmasked previously occult joint disease. In all of our cases, psoriasis improved dramatically with ustekinumab therapy while psoriatic arthritis flared.

Report of Cases
Case 1
A man in his 40s with plaque psoriasis and psoriatic arthritis failed treatment with adalimumab, 40 mg subcutaneously every 2 weeks for 6 months, because of persistent skin disease. After switching to etanercept, 50 mg subcutaneously, twice weekly, both psoriasis and psoriatic arthritis gradually resolved and remained well controlled for several years. When plaque psoriasis flared, treatment was changed to ustekinumab, 90 mg subcutaneously at recommended intervals.10,11 After 1 month of therapy, the plaque psoriasis improved substantially; however, symptoms of psoriatic arthritis became progressively disabling. Some months later, the patient’s joint pains interfered with his activities of daily living. Pain was rated subjectively as 9 of 10. As deterioration worsened, ustekinumab treatment was discontinued. Treatment with etanercept, 50 mg subcutaneously twice weekly, was reinstated. A month after these therapeutic changes, psoriasis and psoriatic arthritis were asymptomatic.
Case 2
A man in his 50s with psoriasis and no history of psoriatic arthritis received consecutive trials of etanercept, 50 mg subcutaneously twice weekly for 8 months, and adalimumab, 40 mg subcutaneously every 2 weeks for 12 months. In both instances, improvement occurred initially, but flares of plaque psoriasis led to discontinuation of the drug. In late 2010, a standard regimen of ustekinumab, 45 mg subcutaneously, was started. Despite clearing of papulosquamous activity, severe migratory arthritis involved the patient’s ankles, knees, elbows, back, and jaw. After 8 months of treatment with ustekinumab, the patient could barely walk 2 city blocks and required a cane for ambulation. Ustekinumab therapy was discontinued, and treatment with adalimumab, 40 mg subcutaneously every 2 weeks, was restarted in conjunction with methotrexate, 10 mg by mouth weekly. A month later, arthritis was barely perceptible, progressing to a sustained remission.

Case 3
A man in his 60s with plaque psoriasis and psoriatic arthritis was effectively treated with etanercept, 50 mg subcutaneously twice weekly, for several years before increasing plaque disease recurred. He was switched to adalimumab, 40 mg subcutaneously every 2 weeks, until he opted for a "drug holiday" during a long period of disease remission. Plaque psoriasis reappeared, and adalimumab was resumed; however, his worsening skin disease was resistant to therapy. Nonetheless, psoriatic arthritis remained quiescent and ustekinumab, 45 mg subcutaneously, was initiated for recalcitrant plaque psoriasis. Although the plaque psoriasis was clear by about 5 months later, diffuse aching of joints required over-the-counter pain medication. Fearing a recurrence of skin disease, the patient elected to remain on a regimen of ustekinumab, controlling joint discomfort with a nonsteroidal anti-inflammatory drug (NSAID) therapy, (diclofenac, 50 mg 3 times a day).

Case 4
A man in his 40s with plaque psoriasis and no history of psoriatic arthritis had been quite comfortable with topical remedies and narrowband UV-B (NB-UVB) therapy. Waning efficacy led to a reconsideration of treatment options. Since anti-TNF therapy was contraindicated because a relative of the patient had multiple sclerosis, a standard regimen of ustekinumab, 45 mg subcutaneously, was initiated. His skin disease improved dramatically during the first month. The NB-UVB therapy was discontinued after 16 weeks (3 injections). Within a few months, the patient noted mild but disturbing migratory arthritis affecting his wrists, elbows, and knees. The joint symptoms were managed with over-the-counter NSAIDs alone. After 1 year of treatment, recalcitrant pinpoint skin lesions unexpectedly appeared on the lower extremities. Despite these symptoms, the patient elected to continue therapy with ustekinumab and topical steroids for low-grade plaque psoriasis, along with NSAID therapy to control joint disease. It is also noteworthy that Dupuytren contractures of 15 years’ duration worsened remarkably after the patient started ustekinumab therapy.

Discussion
There has been 1 phase 2 randomized placebo-controlled trial and 2 phase 3 randomized placebo-controlled trials of ustekinumab therapy for psoriatic arthritis.12 In the phase 2 study, 146 patients were randomly assigned to either group 1, receiving ustekinumab, 90 mg subcutaneously weekly for 4 doses, followed by placebo at weeks 12 and 16; or, group 2, receiving placebo weekly for 4 doses, followed by ustekinumab, 90 mg subcutaneously at weeks 12 and 16. The primary end point was a 20% improvement at 12 weeks using the American College of Rheumatology criteria (ACR20) with both 50% (ACR50) and 70% (ACR70) responses representing secondary end points. At 12 weeks, a greater proportion of group 1 met both the primary end point, as well as the ACR50 secondary end point. At 24, 28, and 36 weeks, patients in group 2 had responses similar to those of group 1. Of note, 21% of the patients terminated study participation, and 16% discontinued the study drug by week 36. Another important component to this trial is that 20% of patients in group 1 and 21% in group 2 continued therapy with stable doses of methotrexate throughout the study.32 Preliminary data from 2 phase 3 multicenter, double-blind, placebo-controlled clinical trials of ustekinumab in psoriatic arthritis were presented at the ACR annual meeting in November 2012. The trials included 927 patients with psoriatic joint disease who were randomized to receive ustekinumab, 45 mg subcutaneously, 90 mg subcutaneously, and placebo at weeks 0, 4, and every 12 weeks thereafter. Patients were permitted to continue stable doses of methotrexate. The primary end point was ACR20 at 24 weeks, but patients in the first trial were followed through week 52. At 24 weeks, ustekinumab significantly reduced the signs and symptoms of arthritis compared with those receiving placebo and at week 52, ustekinumab continued to reduce signs and symptoms or arthritis.13-15 The 3 trials did not comment on flares in psoriatic arthritis in the study patients.

We report 4 cases of psoriasis in which psoriatic arthritis either failed to improve or appeared after a patient taking a TNF blocker was switched to ustekinumab treatment (Table). To our knowledge, there is only 1 other published case series describing similar findings. Stevenson and Markowitz16 reported 3 patients with psoriasis and psoriatic arthritis who were switched to ustekinumab treatment after reduced efficacy associated with an anti-TNF drug. All 3 patients experienced improvement in psoriasis but developed flares of psoriatic arthritis after switching to ustekinumab treatment. The authors16 speculate that TNF may play a greater role in the pathogenesis of joint injury than IL-12 and IL-23, explaining the better response of psoriatic arthritis treated with either anti-TNF or anti-TNF receptor blockade drugs. Another explanation is that greater doses of ustekinumab may be needed to suppress psoriatic arthritis. In this study, 1 patient who switched back to infliximab monotherapy experienced improvements in psoriatic arthritis, but psoriatic skin lesions persisted. The second patient continued therapy with ustekinumab, but methotrexate was added, and the third patient was switched back to etanercept. The authors do not comment on the course of disease following the treatment alteration in the latter 2 patients.16
In the placebo-controlled study of ustekinumab for treatment of psoriatic arthritis, roughly 20% of patients continued methotrexate therapy.15 By contrast, the 4 patients reported in our case series and the 3 presented by Stevenson and Markowitz16 were receiving ustekinumab monotherapy when they developed flares of arthritis. The potential risk of aggravating or unmasking joint disease when switching a patient with known psoriatic arthritis to ustekinumab monotherapy is an unmistakable caveat associated with these 2 case series. The combination of ustekinumab and methotrexate provides a potential explanation as to why patients in the placebo-controlled study did not show an increase in psoriatic arthritis flares.17 Furthermore, methotrexate may be useful as a combination therapy with ustekinumab to ameliorate psoriatic arthritis symptoms.

In our series, patients 2 and 4 had no history of psoriatic arthritis. It is possible that the anti-TNF therapy was controlling their joint disease until therapy with ustekinumab was initiated. This underscores another potential risk of ustekinumab monotherapy in patients who have received TNF blockers even in the absence of clinical joint disease. Since there is no way to predict which patients are at risk for unmasking of psoriatic arthritis once they are switched to ustekinumab therapy, educating health care providers and patients to recognize the symptoms and signs of joint disease seems essential.

One other unexplained, but interesting, observation associated with switching between biologic agents in our series relates to the amplified efficacy of anti-TNF drugs following ustekinumab therapy. Two of our 4 patients restarted treatment with anti-TNF agents after failing treatment with ustekinumab. Prior to ustekinumab therapy, both patients developed extensive new psoriasis activity while on anti-TNF drug therapy; however, following ustekinumab withdrawal, resuming treatment with the same “failed” anti-TNF drug led to rapid improvements in both the skin and joint disease. There are minimal data on switching between biologic agents in patients with psoriasis and psoriatic arthritis. In our case series the mechanism of improved efficacy to a previously failed TNF blocker after discontinuing ustekinumab therapy remains uncertain.

The number of patients with psoriasis receiving ustekinumab therapy continues to rise. Although we report a small case series of arthritis flares after ustekinumab monotherapy, future studies are warranted to better characterize the role of this drug. Since there is no way to predict those at risk for psoriatic arthritis in the setting of ustekinumab therapy, educating health care providers and patients to recognize the symptoms and signs of this destructive, inflammatory joint disorder is essential.

ARTICLE INFORMATION

Author Contributions: Drs Stamell and Cohen and Ms Kutner had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Stamell, Viola, Cohen. Acquisition of data: Stamell, Kutner, Cohen. Analysis and interpretation of data: Stamell, Cohen. Drafting of the manuscript: Stamell, Viola, Cohen. Critical revision of the manuscript for important intellectual content: Stamell, Kutner. Statistical analysis: Cohen. Administrative, technical, or material support: Cohen. Study supervision: Stamell, Cohen.

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**NOTABLE NOTES**

### The Importance of Being Fragrant

Dylan Waterman, BS; Scott A. Norton, MD, MPH

*They would often strip me naked from top to toe, and lay me at full length on their bosoms; wherewith I was much disgusted because, to say the truth, a very offensive smell came from their skins ... I conceive that my sense was more acute in proportion to my littleness, and that those illustrious persons were no more disagreeable to their lovers, or to each other, than people of the same quality are with us in England.*

(John Lemuel Gulliver, Brobdingnag, 1703)

While tiny Gulliver’s experience resting on the pungent chests of the ladies of Brobdingnag serves as a fairly extreme example, this passage from Jonathan Swift’s *Gulliver’s Travels* illustrates one of the skin’s most complex characteristics: its odor.

Humans are the world’s least hairiest apes, yet have glands associated with each hair follicle that collectively contribute to each person’s unique aroma. While eccrine glands secrete a watery solution directly onto the skin to aid in evaporative cooling, sebaceous and apocrine glands empty their products into minuscule spaces surrounding each hair shaft. Sebaceous glands remain largely dormant until puberty, when sebum production increases dramatically. Odorless when first secreted, sebum is broken down into fatty acids by commensal bacteria to produce a strong, sweaty fragrance. These glands are found throughout the body, from toe-top to eyelid, and are most abundant on the facial skin and the scalp.

Conversely, apocrine glands are found exclusively in regions such as the armpit, external genitalia, and perianal area, and are responsible for the dominant note among the components of healthy human body odor. The axillae in particular define each person’s particular scent. Curiously, the development of axillary glands varies among races. Many people of northeast Asian descent, for example, have fewer and less active axillary apocrine glands—many have barely any axillary odor at all. In addition to the density of glands in the axillae, the diversity and abundance of the axillary microflora contribute to the quality and potency of an individual’s scent.

Research on axillary secretions, in addition to urine and saliva, has revealed myriad odoriferous steroid compounds. Nevertheless, the precise composition of body odor remains mysterious, although it is well recognized that humans possess highly individualized odors discernible by both animals and fellow *Homo sapiens*. Whereas each human typically regards his or her own bodily scent as pleasant, people generally find the scent of other humans disagreeable. In this sense, odor helps to distinguish between “self” and “non-self,” and may contribute to preferential interactions with other humans (mate choices, for example). While rarely as off-putting as the smell of Brobdingnag’s courtly ladies, individual fragrance is one of humanity’s unique, defining features. Its significance is certainly nothing to turn your nose up at.

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