Abstract

As summarized in Part I of this continuing medical education article, the currently available epidemiologic data suggest that psoriasis may be a risk factor for cardiometabolic disease. Emerging data also suggest associations between psoriasis and other comorbidities beyond psoriatic arthritis, including chronic kidney disease, inflammatory bowel diseases, hepatic disease, certain malignancies, infections, and mood disorders. Recognizing the comorbid disease burden of psoriasis is essential for ensuring comprehensive care of patients with psoriasis. The clinical implications of the comorbid diseases that are associated with psoriasis and recommendations for clinical management are reviewed in this section.

Cardiometabolic Disease

- Patients with psoriasis are underscreened and undertreated for cardiovascular (CV) risk factors.
- At a minimum, patients with psoriasis should be screened for CV risk factors according to recommendations for the general adult population.
- Observational data suggest that treatment with methotrexate or tumor necrosis factor (TNF) inhibitors is associated with a decrease in CV events; however, data from randomized controlled trials (RCTs) are not yet available, and data for other psoriasis therapies are lacking.

In spite of the evidence supporting an increased prevalence of CV risk factors and increased risks of CV disease (CVD) and mortality among patients with psoriasis, data suggest that patients are inadequately screened and undertreated for CV risk factors.[1-5] For example, in a cross-sectional study of National Ambulatory Medical Care Survey data from 2005 to 2009, only 41% of patients with psoriasis versus 66% of those without psoriasis were screened for at least one CV risk factor (blood pressure, glucose, cholesterol, or body mass index [BMI]).[4] Specifically among dermatologists, screening for CV risk factors was infrequent (blood pressure 2.6%, glucose 1.2%, cholesterol 4.3%, and BMI 9.7%). Similarly, a survey of 127 United States (U.S.) dermatologists in 2015 revealed that less than 50% screened for hypertension, dyslipidemia, or diabetes in patients with psoriasis.[5] Furthermore, in a cross-sectional study of patients with hypertension in the United Kingdom (U.K.), patients with psoriasis were more likely to have uncontrolled hypertension compared with patients without psoriasis.[3] Together, these data highlight an important healthcare systems gap in screening for and treating CV risk

factors among patients with psoriasis. Therefore, as recommended by clinical practice guidelines,[6,7] dermatologists should, at a minimum, advise patients with moderate-to-severe psoriasis of their possible increased risk of CVD and recommend that they see their primary care physician for appropriate medical screenings and assessment.

Major Adverse Cardiovascular Events (MACE)

Screening for CV risk factors among patients with psoriasis, particularly those with more severe disease, is essential to minimizing risk of MACE. Screening and management of CV risk factors in patients with psoriasis should, at a minimum, follow recommendations for the general adult population (level of evidence IB).[6-8] Furthermore, lifestyle interventions such as weight loss and smoking cessation should be encouraged among psoriasis patients who are obese and current smokers (level of evidence IB). Per the American College of Cardiology and American Heart Association guidelines, CV risk assessment should include evaluation of traditional risk factors every four to six years among persons aged 20-79 and estimation of 10-year risk among those aged 40-79 (Table I).[9]

Important questions that remain unanswered include what the particular CV risk factor treatment goals should be for psoriasis patients and whether the presence of psoriasis alone warrants different and/or more aggressive screening and management strategies for CV risk factors compared with the general population. Mehta et al.'s study of the impact of psoriasis on the Framingham Risk Score found that the addition of psoriasis warranted a change in CV risk factor treatment plans and goals for over 60% of patients.[10] Thus, psoriasis itself, especially severe disease, may indeed necessitate clinically significant changes in prevention and treatment

goals for CV risk factors in a similar manner to what has been recommended by the European League Against Rheumatism for patients with rheumatoid arthritis (RA).[11]

Critically, it remains unknown if successful treatment of psoriasis will lower the risk of future CV events. Currently treatment of psoriasis is considered elective, and systemic treatments are reserved for patients with severe disease that is physically or psychologically disabling to the patient. As a result, the overwhelming majority of patients, even with objectively severe psoriasis, do not receive adequate treatment to control their skin disease.[12-14] This view of psoriasis may be similar to that of hypertension in the 1960s when treatment was considered elective and potentially harmful in the elderly until RCTs demonstrated improved CV outcomes and decreased mortality among those receiving antihypertensive therapy.[15,16] Unlike hypertension, there are currently no RCTs to prove that psoriasis therapies lower the risk of CVD. Meta-analyses of observational studies suggest that methotrexate and TNF inhibitors may lower the risk of CV events in RA patients.[17-19] Similarly, emerging data from observational studies of psoriasis suggest that methotrexate and TNF inhibitors may lower the risk of CV events in psoriasis patients;[20-22] however not all studies have observed a protective effect,[23,24] and the observational nature of the studies limits the conclusions that can be drawn. Mixed results from studies of psoriasis therapy effects on risk of CV events, which have also been observed in the RA population, may be due to differences in study design, uses of different comparator groups, and misclassification of treatment status, and they highlight the need for RCTs to better address this question.[25] Thus, RCTs of psoriasis therapy effects on CVD using rigorous surrogate markers such as vascular inflammation[26,27] and, ultimately, on CV events are essential. Initial studies in RA[28] and psoriasis[29] suggest that TNF inhibitors may reduce vascular inflammation as measured by 18-fluorodeoxyglucose positron emission tomography-computed tomography.

Multiple studies are ongoing to evaluate the effects of ultraviolet B phototherapy (ClinicalTrials.gov identifier NCT01553058), TNF inhibition (NCT01553058, 01866592), interleukin (IL) 12/23 inhibition (NCT02187172), and IL17 inhibition (NCT02690701) on vascular inflammation. Finally, underscoring the importance of testing the inflammatory hypothesis in CVD, the Cardiovascular Inflammation Reduction Trial (CIRT) (NCT01594333) is an ongoing RCT studying the effect of methotrexate on the incidence of MACE in patients with type 2 diabetes or metabolic syndrome who have had prior MI.[30] Though the CIRT trial is not a study of psoriasis patients, it will be important in establishing whether methotrexate treatment of inflammation reduces the residual risk of CVD. If these or other future RCTs reveal a protective effect of psoriasis treatments on CVD, a paradigm shift in the current view of psoriasis therapy will be needed, and support for a causal relationship between psoriasis and CVD would be strengthened.

Obesity

Obesity may have important effects on psoriasis severity and response to therapies. The impact of weight loss interventions, either diet modification or exercise, on psoriasis severity was assessed in a systematic review and meta-analysis of seven RCTs of 878 participants.[31] The meta-analysis of three RCTs found a significantly greater reduction in the Psoriasis Area and Severity Index (PASI) score among patients receiving the weight loss intervention than those who did not receive the intervention (pooled mean PASI difference -2.49, 95% confidence interval [CI] -3.90 to -1.08). Similarly, among four studies that assessed 75% reduction in the PASI score (PASI-75) as an outcome, more participants in the intervention versus the control group achieved PASI-75 (pooled odds ratio [OR] 2.92, 95% CI 1.39-6.13). Thus, current data

suggest that weight loss improves psoriasis, though the clinical significance is modest. However, there was at least substantial heterogeneity among the studies included in the meta-analyses, therefore, additional studies are needed to better understand the effects of specific weight loss interventions on psoriasis.

Increased weight and BMI may also negatively impact response to systemic treatments including biologic therapies and cyclosporine. Sub-analyses of data from RCTs have found that higher weight or BMI is associated with poorer response to fixed dose biologic therapies (i.e., adalimumab, etanercept, and ustekinumab 45mg dose), whereas the response to infliximab, whose dose is weight-based, does not vary with BMI.[32,33] A U.S. cross-sectional study of psoriasis patients seen in the routine clinical setting supports the RCT findings.[34] The likelihood of having clear or almost clear skin as defined by a six-point Physician Global Assessment was found to decrease with increasing BMI among psoriasis patients on adalimumab or etanercept but not among those on methotrexate. Together, these data suggest that obese psoriasis patients may be underdosed with fixed dose biologics. Importantly, weight loss may improve response to biologic therapy as suggested by a single RCT evaluating the effect of weight reduction by diet modification on treatment efficacy among obese psoriasis patients on adalimumab, etanercept, infliximab, or ustekinumab.[35] Another similarly designed RCT also found improved response to treatment with low-dose cyclosporine among obese psoriasis patients randomized to a low-calorie versus normal diet.[36] While weight has not been found to have an effect on response to treatment with methotrexate, one single center study suggests that obese psoriasis patients are more likely to experience loss of response to methotrexate than non-obese patients.[37]

Lastly, obese patients with psoriasis may be at increased risk of medication side effects from methotrexate. Nonalcoholic fatty liver disease (NAFLD) is a relative contraindication to

methotrexate and is more common among obese patients.[38,39] Being overweight may also be a risk factor for severe hepatic fibrosis among psoriasis patients on methotrexate.[40] Thus, it has been recommended that obese psoriasis patients on methotrexate undergo more aggressive monitoring, including liver biopsies both at baseline (within two to six months of starting therapy) and at a cumulative dose of 1.0-1.5g of methotrexate.[38]

Collectively, these data highlight the importance of providing counseling to overweight and obese patients with psoriasis about weight loss and the impact of their weight on both psoriasis severity and treatment response (level of evidence IB). Furthermore, dermatologists should be cautious of methotrexate use in obese psoriasis patients.

Hypertension

Given the association between psoriasis and hypertension, patients with psoriasis should undergo at least standard blood pressure screening that is recommended for the general population (Table II).[41] As data suggest that psoriasis patients with hypertension may have more severe hypertension[42] and may be more likely to have poorly controlled blood pressure than hypertensive patients without psoriasis,[3] appropriate management and monitoring of blood pressure is important to emphasize. Lastly, since hypertension is a well-known potential adverse effect of cyclosporine, dermatologists should use cyclosporine cautiously in psoriasis patients with pre-existing hypertension.[43]

Diabetes

As psoriasis is associated with an increased risk of diabetes, patients with psoriasis should be screened for diabetes at least per standard recommendations for the general population

(Table III).[44-47] Based on observational data that suggest more aggressive diabetes[48] and greater prevalence and risk of micro- and macrovascular complications[49,50] among patients with than without psoriasis, it may be reasonable to consider more frequent monitoring of diabetes and screening for diabetic complications among psoriasis patients. However, additional studies are needed to support these initial findings and before widespread implementation of such recommendations.

Dyslipidemia

More prevalent dyslipidemia among patients with psoriasis supports lipid screening at least per standard recommendations for the general population (Table I). Hyperlipidemia is a potential adverse effect of treatment with acitretin[51] and cyclosporine;[43] therefore these medications should be used with caution in psoriasis patients with dyslipidemia, and close lipid monitoring is necessary.

In summary, it is essential for both clinicians and patients to understand the possibly heightened risk of CVD in psoriasis patients, which may increase with disease severity and duration. At a minimum, screening for and management of CV risk factors in psoriasis patients should be according to the recommendations for the general adult population (Tables I-III).[6,7] Continued basic, translational and epidemiologic research will be essential to support the development of evidence-based psoriasis-specific recommendations for co-morbid disease screening and management. Additionally, ongoing and future well-conducted RCTs will be necessary to answer the critical question of whether or not treatment of psoriasis, itself, has an effect on CVD, events, morbidity and mortality.

Gastrointestinal Disease

- Adalimumab and infliximab are FDA approved for treatment of both psoriasis and Crohn's disease (CD) and ulcerative colitis (UC), respectively.
- Secukinumab and ixekizumab should be used with caution in patients with both psoriasis and CD.
- Methotrexate and acitretin should be used cautiously in patients with psoriasis and liver disease.
- TNF inhibitors should be avoided in patients with psoriasis and moderate-to-severe alcoholic hepatitis

Inflammatory Bowel Disease

It is important to understand the therapeutic implications of comorbid inflammatory bowel disease (IBD) which is more prevalent among patients with than without psoriasis. Adalimumab and infliximab are FDA approved for the treatment of both psoriasis and IBD (CD and UC) and are, thus, the treatments of choice in patients with both conditions. Ustekinumab, while not currently FDA-approved for the treatment of IBD, has been reported in phase III RCTs to be efficacious in both the initial treatment of and maintenance therapy for moderate-to-severe CD that is resistant to TNF inhibitor therapy.[52] Notably, dosing of systemic medications for treatment of CD and UC is often higher than that for psoriasis. Unexpectedly, secukinumab, an IL17A inhibitor and recently FDA-approved biologic for the treatment of moderate-to-severe psoriasis, was not only found to be ineffective for treatment of CD but was also suggested to be associated with higher adverse event rates than placebo in a single clinical trial.[53] Furthermore,

exacerbations of CD were observed in clinical trials of secukinumab[54] and ixekizumab[55] for the treatment of psoriasis and should, therefore, be used with caution in patients with both psoriasis and CD.

Hepatic Disease

The greater prevalence of NAFLD among patients with psoriasis suggests cautious use of potentially hepatotoxic medications such as methotrexate and acitretin in patients with both diseases. As discussed previously, NAFLD is a relative contraindication to treatment with methotrexate, and more aggressive monitoring with liver biopsies at baseline and at a cumulative dose of 1.0-1.5g of methotrexate may be considered (level of evidence IV).[38] Noninvasive tests to detect hepatic fibrosis such as various serologic tests and radiologic imaging such as ultrasound-based elastography, magnetic resonance elastography, acoustic radiation force impulse imaging, and cross-sectional imaging have also been suggested as promising tools but have yet to be established in the setting of long term methotrexate use among psoriasis patients.[56]

Moderate-to-severe alcoholic hepatitis is a relative contraindication to treatment with TNF inhibitors, specifically etanercept. In a single RCT of etanercept in the treatment of moderate-to-severe alcoholic hepatitis, higher mortality and serious infection rates at six months were detected in the etanercept versus placebo group.[57] Thus, etanercept and other TNF inhibitors should be avoided in psoriasis patients with moderate-to-severe alcoholic hepatitis (level of evidence IB). Importantly, patients with psoriasis, especially those being considered for systemic treatment with potentially hepatotoxic medications, should be screened for alcohol use and counseled appropriately.

Chronic Kidney Disease

- Patients with more severe psoriasis may warrant closer monitoring for kidney disease, and potentially nephrotoxic medications such as cyclosporine should be used with caution.

With data suggesting increased risks of chronic kidney disease and end-stage renal disease among patients with psoriasis,[58,59] the risks versus benefits of treating patients with moderate-to-severe psoriasis with potentially nephrotoxic medications such as cyclosporine should be carefully considered. Closer monitoring for renal insufficiency with serum creatinine, blood urea nitrogen, and urinalysis to screen for microalbuminuria may also be considered for patients with psoriasis affecting >3% of their body surface area (BSA) (level of evidence III).

Malignancy

- TNF inhibitors may be associated with increased risks of non-melanoma skin cancer (NMSC) and melanoma.
- Chronic oral psoralen and ultraviolet A (PUVA) treatment is associated with an increased risk of NMSC, particularly squamous cell carcinoma (SCC).
- Patients with psoriasis on immunosuppressive therapy should adhere to guidelines for age-appropriate cancer screening.
- Annual skin cancer screening may be considered in psoriasis patients receiving immunosuppressive medications or phototherapy.

Risk of malignancy among patients with psoriasis is most convincing for lymphoma, particularly cutaneous T cell lymphoma (CTCL),[60-62] though misdiagnosis of CTCL as psoriasis may at least partially explain this association. Increased risks of other cancers have also been suggested.[63] Malignancy risk is of special concern among patients treated with immunosuppressive systemic therapies or phototherapy. Most studies to date have assessed malignancy risk due to TNF inhibitors received by patients with RA or a combination of immune-mediated diseases (i.e., RA, IBD, psoriatic diseases, or ankylosing spondylitis) for which TNF inhibitors are indicated. Meta-analyses of RCTs[64] and observational studies[65] of patients on TNF inhibitors found no increased risk of internal malignancy but suggested that risks of NMSC[64,65] and melanoma[65,66] may be increased. Skin cancer is also of particular concern among patients who have received phototherapy. The evidence is strongest for an increased risk of NMSC, particularly SCC, among patients treated with PUVA therapy whereby treatment with >200 sessions of PUVA is associated with a 14-fold increased risk of SCC.[67] The risk of melanoma with oral PUVA remains controversial, and increased risk of skin cancer with topical PUVA or narrow-band ultraviolet B remains unproven.[68]

Especially considering the potential cancer risks and malignancy warnings that accompany adalimumab, etanercept, infliximab, and ustekinumab, it is important that clinicians recommend and patients adhere to age-appropriate cancer screening (Table IV). Screening and appropriate counseling for important behavioral risk factors for cancer (e.g. smoking) is also suggested, and at least yearly skin cancer surveillance may be considered (level of evidence III-IV). Importantly, malignancy, other than NMSC, is at least a relative contraindication for treatment with immunosuppressive therapies for psoriasis. Guidelines for treatment of RA indicate that treatment with biologics may be cautiously considered in patients with history of

malignancy if they have been cancer-free for at least five years (level of evidence III-IV).[69,70] Among psoriasis patients with multiple NMSCs, acitretin may be considered for both psoriasis treatment and its potential chemopreventive effects.[71,72] Lastly, skin biopsy should be considered in psoriasis patients with atypical lesions or disease that fails to appropriately respond to treatment in order to rule out CTCL.

Infection

- Screening for hepatitis B and C, and human immunodeficiency virus (HIV) should be considered prior to starting immunosuppressive therapy in patients with psoriasis.
- Screening for tuberculosis (TB) prior to and annually during immunosuppressive therapy in patients with psoriasis is recommended.
- Patients with psoriasis are recommended to keep up to date with vaccinations ideally prior to receiving immunosuppressive therapies.

Infection risk attributable to psoriasis, itself, and immunosuppressive therapies used to treat moderate-to-severe disease remains a matter of debate. Observational studies suggest increased risks of serious infections including pneumonia among patients with psoriasis. Both meta-analyses of RCTs and observational studies have not found higher risks of serious infection due to TNF inhibitors compared with other systemic therapies; the effects of specific psoriasis treatments on serious infection risk remain unclear. An observational study of psoriasis patients suggests that risk of herpes zoster may be increased among patients receiving combination biologic and methotrexate therapy.[73] Considering the serious infection warnings that accompany methotrexate, cyclosporine, adalimumab, etanercept, infliximab, ustekinumab, secukinumab, and

ixekizumab, it is recommended that psoriasis patients, particularly those requiring immunosuppressive systemic therapy, remain up-to-date with their vaccinations per the Advisory Committee for Immunization Practices (level of evidence IV).[74-76] Since respiratory infections were found to be the most common serious infections in patients with psoriasis,[77,78] influenza and pneumonia vaccinations may be particularly important. Live vaccines should be avoided in patients currently on and within at least one month of receiving immunosuppressive therapy.[74]

Infections of special concern, especially in the setting of treatment with immunosuppressive systemic medications, include viral hepatitis B and C, HIV), and TB. The Center for Disease Control and Prevention (CDC) and the Medical Board of the National Psoriasis Foundation recommend screening all patients for hepatitis B infection prior to initiating immunosuppressive therapy with triple serology and baseline liver function tests.[79,80] Screening for hepatitis C is more controversial but several guidelines recommend screening at least high risk populations prior to initiating immunosuppressive (particularly biologic) therapy.[81-83] The CDC also recommends at least one HIV screening test in every person between the ages of 13 and 64.[84] Finally, considering the potential for TB reactivation particularly with TNF inhibition, whereby the greatest risk may be associated with adalimumab and infliximab,[85,86] TB screening prior to starting and annually while on biologic therapy has been recommended (level of evidence IV).[87]

Mood Disorders

- Screening for mood disorders should be considered in patients with psoriasis, particularly those with more severe disease.

Reports of increased risks of depression, anxiety, and suicidality among patients with psoriasis[88,89] suggest that clinicians should consider screening psoriasis patients for depression and suicidality, especially if they have more severe disease. As both acitretin and apremilast have been labeled with warnings for mood changes and depression, respectively, patients on these medications should be monitored for depression or other mood instability (level of evidence III).

Psoriatic Arthritis

- All patients with psoriasis should be screened for psoriatic arthritis (PsA).
- The presence of PsA is an indication for systemic therapy.

PsA is associated with decreased functional ability and quality of life and may result in permanent joint damage. A diagnosis of PsA is an indication for treatment with systemic therapy. Early detection and treatment is essential to prevent progression of this potentially debilitating joint disease.[90] All patients with psoriasis should be asked if they have joint symptoms including joint swelling, tenderness, and morning stiffness that lasts for at least 30 minutes and improves with activity (level of evidence III-IV). Diagnostic tests and treatment recommendations are reviewed in more detail elsewhere.[91-93]

In conclusion, clinicians and patients must understand the wide range of medical comorbidities associated with psoriasis in order to ensure respective provision and receipt of appropriate screening and treatment in an attempt to reduce morbidity and mortality. Importantly, ongoing and future well-conducted RCTs are necessary to determine the effect of

379 psoriasis treatment on the associated risks of cardiometabolic, renal, malignant, infectious,

380 psychiatric, and other emerging comorbid diseases.

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Abbreviations and Acronyms

BMI	Body mass index
BSA	Body surface area
CD	Crohn's disease
CDC	Centers for Disease Control and Prevention
CI	Confidence interval
CIRT	Cardiovascular Inflammation Reduction Trial
CT	Computed tomography
CTCL	Cutaneous T cell lymphoma
CV	Cardiovascular
CVD	Cardiovascular disease
FDA	Federal Drug Administration
FOBT	Fecal occult blood test
HIV	Human immunodeficiency virus
IBD	Inflammatory bowel disease
IL	Interleukin
MACE	Major adverse cardiovascular event

NAFLD	Nonalcoholic fatty liver disease
NMSC	Non-melanoma skin cancer
OR	Odds ratio
PASI	Psoriasis Area and Severity Index
PUVA	Psoralen and ultraviolet A
RA	Rheumatoid arthritis
RCT	Randomized controlled trial
SCC	Squamous cell carcinoma
TB	Tuberculosis
TNF	Tumor necrosis factor
UC	Ulcerative colitis

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CME Questions:

A 55 year old obese male presents with plaque psoriasis with 15% BSA involvement. His medical history is remarkable for diabetes, chronic kidney disease, Crohn's disease, and a history of optic neuritis. Current medications include lisinopril and insulin. He is a current smoker with a 35 pack-year smoking history and drinks six alcoholic drinks per week.

1. Which of the following is the most appropriate and likely to be effective treatment:

    a. Methotrexate

    b. Apremilast

    c. Adalimumab

    d. Ustekinumab

    e. Secukinumab

Answer: d

2. You decide to start a biologic therapy. Which of the following evaluations or interventions is not appropriate at this time?

    a. Hepatitis B serologies

    b. Pneumococcal vaccine

    c. Chest x-ray

d. Weight-loss counseling

e. Low-dose chest CT

Answer: c