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REVIEW ARTICLE

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Underdiagnosed and undertreated psoriasis: Nuances of treating psoriasis affecting the scalp, face, intertriginous areas, genitals, hands, feet, and nails

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Abstract

Psoriasis of the scalp, face, intertriginous areas, genitals, hands, feet, and nails is often underdiagnosed, and disease management can be challenging. Despite the small surface area commonly affected by psoriasis in these locations, patients have disproportionate levels of physical impairment and emotional distress. Limitations in current disease severity indices do not fully capture the impact of disease on a patient's quality of life, and, combined with limitations in current therapies, many patients do not receive proper or adequate care. In this review, we discuss the clinical manifestations of psoriasis in these less commonly diagnosed areas and its impact on patient quality of life. We also examine clinical studies evaluating the effectiveness of therapies on psoriasis in these regions. This article highlights the need to individualize treatment strategies for psoriasis based on the area of the body that is affected and the emerging role of biologic therapy in this regard.

KEYWORDS

clinical studies, difficult to treat psoriasis, intertriginous, nails, palmoplantar, psoriasis, psoriasis of the extremities, quality of life, review, scalp, treatment options

1 | INTRODUCTION

Psoriasis is a chronic inflammatory skin disorder that affects approximately 3% (7.4 million) of the adult population in the United States (Rachakonda, Schupp, & Armstrong, 2014). The pathogenesis of psoriasis is characterized by increased production of inflammatory cytokines that cause hyperkeratosis (Lowes, Suárez-Fariñas, & Krueger, 2014). Briefly, interleukin (IL)-23 and IL-12 are produced by myeloid dendritic cells, and these cytokines activate naïve T cells to differentiate into Th1, Th17, and Th22 cells, which then produce cytokines responsible for the development of psoriatic plaques such as IL-17, IL-22, tumor necrosis factor-α, and interferon-γ (Lowes et al., 2014). Cutaneous lesions most commonly develop on the elbows, knees, scalp, umbilicus, and lumbar regions, and are typically characterized by erythematous plaques covered with silvery-white scales, termed chronic plaque psoriasis (Schön & Boehncke, 2005). Less frequently, psoriasis can occur on the nails (23–27%), face (49%), palms and soles (12–16%), or intertriginous regions (21–30%), and management of psoriasis in these areas can be challenging (Canpolat, Cemil, Eskioğlu, & Akis, 2008; Merola, Li, Li, Cho, & Qureshi, 2016).

The quality of life (QoL) of patients with psoriasis affecting less common areas may be disproportionately impacted relative to the affected area (Figure 1) (Augustin et al., 2010; Sampogna et al., 2004, 2014). For example, the presence of lesions in highly visible areas can affect a patient's self-esteem, whereas involvement of the palms can make even opening a jar challenging (Janowski, Steuden, & Bogaczewicz, 2014). Nail or hand psoriasis can cause increased financial burdens due to reduced workplace productivity from disease impairment (Augustin et al., 2010; Schmitt & Ford, 2006). Using current scoring systems to measure the severity of psoriasis, such as the Psoriasis Area Severity Index (PASI) and Physician's Global Assessment (PGA), will not capture the substantial impact of disease in these regions because they do not include a specific measurement of these areas nor do they incorporate QoL measures. If using only PASI scores, for example, the location of the skin findings may not be considered and patients can be greatly affected by location versus size alone. Thus, evaluation scales were developed that specifically measure disease impact in these areas such as the Nail Psoriasis and Severity Index (NAPSI) and scalp-modified PASI (S-mPASI). Limitations in the understanding of psoriasis in localized areas may result in undertreatment

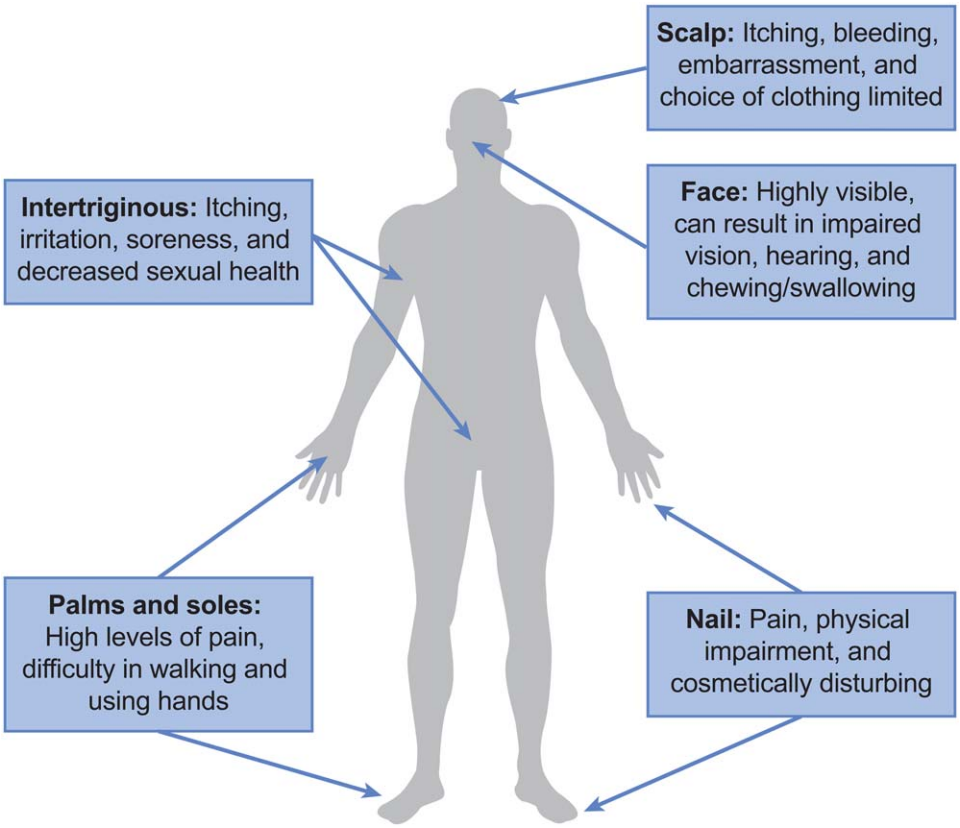

FIGURE 1 Symptoms of psoriasis by body region

and poorer clinical outcomes. Disease management may be further complicated by limitations of current therapies. Topical agents, for example, may not be effective or well tolerated in difficult-to-treat areas of the body, and treatment regimens may be time-consuming, visible, messy, and odorous, and may stain clothing or skin.

This review discusses the clinical manifestations of psoriasis phenotypes (Figure 2a–d) that are less commonly diagnosed and details how presence of disease in these areas impact a patient's QoL. In addition, treatment options will be examined for patients with scalp, face, intertriginous, genital, palmoplantar, and nail psoriasis.

2 | METHODS

PubMed literature searches were conducted with the following terms: psoriasis and face/facial, psoriasis and palmoplantar, psoriasis and intertriginous or inverse, psoriasis and genital, psoriasis and scalp, and psoriasis and nail. Abstracts from English-language articles in the last 10 years were screened for relevance.

2.1 | Scalp

Scalp involvement occurs in 45–56% of individuals with psoriasis (Merola, Li, et al., 2016). It is typically among the first affected areas of the body, with the frequency of lesion formation increasing with disease duration. The diagnosis of scalp psoriasis can be delayed due to overlapping features with other papulosquamous disorders of the scalp, particularly seborrheic dermatitis (Treadwell, 2011). Psoriasis lesions on the scalp are usually asymmetrical and sharply demarcated, and exhibit silvery-white scaling.

The symptoms of scalp psoriasis can result in decreased QoL by causing pain, itching, bleeding, feelings of embarrassment, and restricting clothing choices (Sampogna, Linder, et al., 2014). QoL is more adversely affected in women than men, and individuals younger than 40 years are more adversely affected compared with patients 60 years or older (Sampogna, Linder, et al., 2014).

Common treatment options for patients with scalp psoriasis include topical agents such as vitamin D analogs, corticosteroids, and coal tar. However, these agents are challenging to use on the scalp because hair makes application burdensome, and many patients find them cosmetically unacceptable (Menter et al., 2011). These issues can lead to nonadherence and dissatisfaction with treatment options.

In a recent systematic review of topical therapies for chronic plaque psoriasis of the scalp, vitamin D and corticosteroid combination therapy, and corticosteroid monotherapy were found to be more effective and safer than vitamin D monotherapy (Schlager et al., 2016). However, monotherapy with generic topical steroids may be acceptable for short-term therapy due to the slim efficacy benefit of vitamin D and corticosteroid combination therapy over steroid therapy alone. Targeted phototherapy with an excimer laser can provide an effective alternative to topical therapy when used with a blower device that displaces hair (Menter et al., 2010).

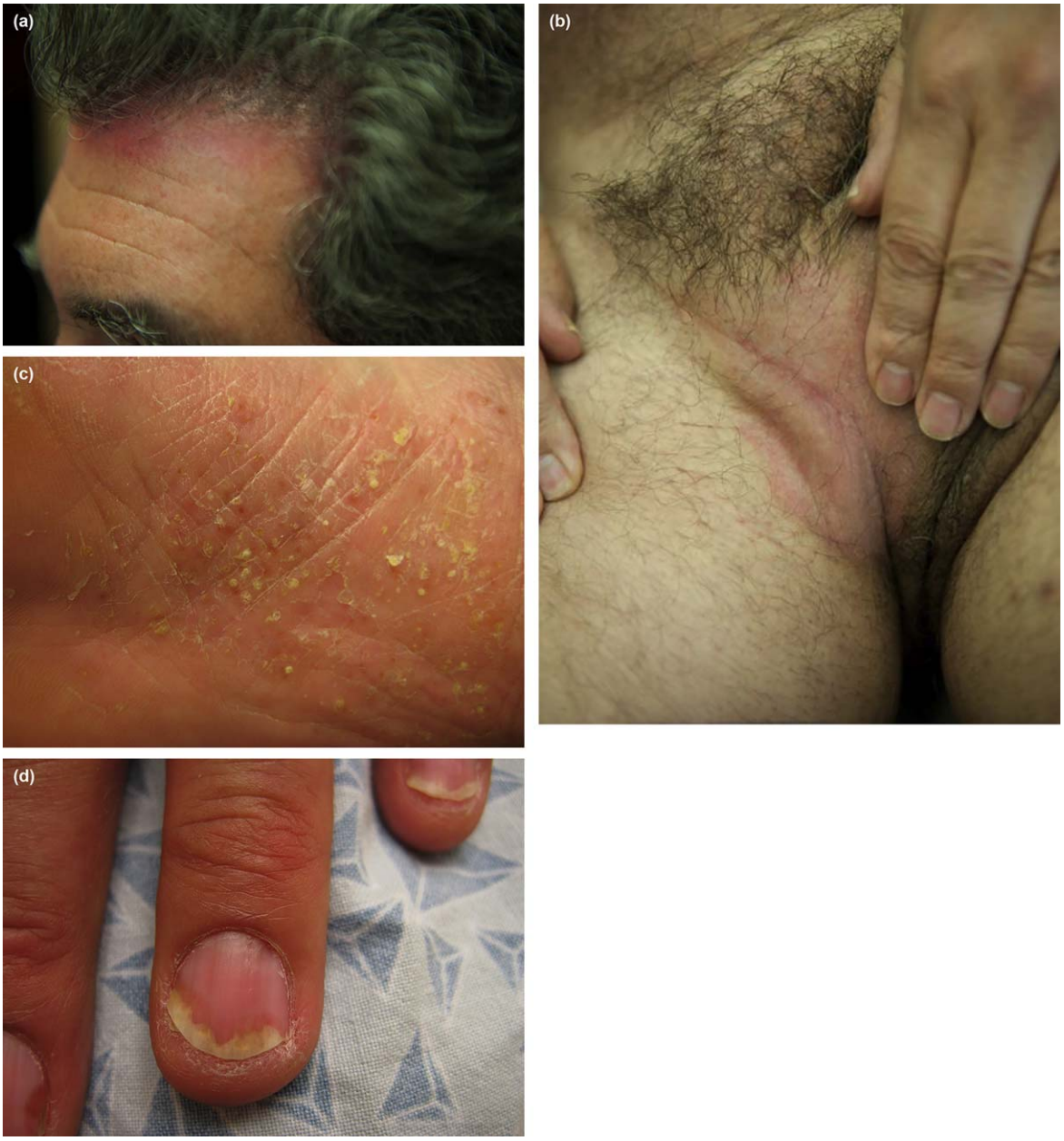

FIGURE 2 Images of psoriasis in underdiagnosed and undertreated areas. (a) Scalp psoriasis (courtesy of Dr Joseph Merola and Dr Abrar Qureshi). (b) Inverse psoriasis of the groin (courtesy of Dr Joseph Merola and Dr Abrar Qureshi). (c) Plantar psoriasis (courtesy of Dr Joseph Merola and Dr Abrar Qureshi). (d) Nail psoriasis (courtesy of Dr Joseph Merola and Dr Abrar Qureshi)

Improvement in scalp psoriasis with systemic agents occurred in trials of etanercept, adalimumab, secukinumab, ixekizumab, and apremilast (Table 1) (Bagel et al., 2012, 2017; Langley et al., 2015; Moore et al., 2007; Paul et al., 2012; Reich et al., 2017; Rich et al., 2016; Thaci, Unnebrink, Sundaram, Sood, & Yamaguchi, 2015; Tyring et al., 2013). Similarly, a recent retrospective cohort study demonstrated the efficacy of infliximab and ustekinumab in addition to etanercept and adalimumab (Fotiadou et al., 2016). Most reports were post hoc analyses of moderate-to-severe plaque psoriasis trials (Langley et al., 2015; Reich et al., 2017; Rich et al., 2016; Thaci et al., 2015). To date, only 1 prospective clinical trial was conducted specifically in patients with moderate-to-severe scalp psoriasis without a requirement to have body-surface-area involvement $\geq$ 10% (Bagel et al., 2017). This placebo-controlled, double-blind, phase 3b trial demonstrated the superiority of secukinumab compared with placebo after 12 weeks of treatment (Bagel et al., 2017).

A large proportion of patients with severe scalp psoriasis presents with minimal chronic plaque psoriasis on the body and, hence, may not receive systemic therapy indicated for moderate-to-severe chronic plaque psoriasis. The adjunctive use of keratolytic and tar-based shampoos, along with topical therapy (steroids and vitamin D analogs), may suffice initially, but long-term compliance can be poor. Localized ultraviolet B therapy using fiber-optic hair brushes is successful for patients, but these devices are expensive and patients need high allowances on

TABLE 1 Selected clinical trials of approved agents for psoriasis in difficult-to-treat areas[a]

Study	Study design	Primary location evaluated	Size, *n*	Treatment	Duration	Results/remarks
Scalp						
Etanercept (TNF-α inhibitor)						
Moore et al. (2007)	Randomized, dose-interruption study	Whole body	2546	Etanercept (50 mg) twice weekly for 12 weeks followed by etanercept once weekly for 12 weeks or discontinuation; the discontinuation group received etanercept once weekly after relapse at week 16 or 20	24 weeks	Discontinuation of etanercept resulted in loss of improvements in PGA of scalp psoriasis. Limited reporting of scalp results
Bagel et al. (2012) and Tyring et al. (2013)	Randomized, double-blind, placebo-controlled trial	Scalp; moderate-to-severe plaque psoriasis with scalp involvement	124	Etanercept (50 mg) twice weekly for 12 weeks followed by once weekly for 12 weeks or placebo twice weekly for 12 weeks followed by etanercept twice weekly for 12 weeks	24 weeks	Etanercept improved PSSI scores at week 12 (mean percent change: etanercept, 87% vs. placebo, 20%; $p < .0001$) PSSI 75 at week 12: etanercept, 86% vs. placebo, 11%. Both groups showed improved PSSI scores at week 24. Patient-reported outcomes of scalp pruritus, scalp pain, DLQI, emotional distress/depression, and treatment satisfaction were also improved
Adalimumab (TNF-α inhibitor)						
Paul et al. (2012)	Randomized, double-blind, vehicle-controlled trial	Subanalysis of phase 3 trial that evaluated moderate-to-severe scalp psoriasis in patients with and without psoriatic arthritis	730	Adalimumab (80 mg) at week 0 and adalimumab (40 mg) every other week for 15 weeks with or without calcipotriol/betamethasone dipropionate (scalp excluded)	16 weeks	Adalimumab improved PSSI, pruritus, and DLQI scores at week 16 regardless of baseline psoriatic arthritis status
Thaci et al. (2015)	Randomized, double-blind, vehicle-controlled trial	Subanalysis of phase 3 trial that evaluated scalp psoriasis in a pooled treatment group (adalimumab with or without calcipotriol plus betamethasone dipropionate) of patients with moderate-to-severe psoriasis	663	Adalimumab (80 mg at week 0; followed by 40 mg every other week from weeks 1–15) in addition to either topical calcipotriol plus betamethasone dipropionate or drug-free vehicle applied once daily for 4 weeks, and as needed thereafter	16 weeks	Median decrease from baseline PSSI at week 16 of 100% with adalimumab. Improvements in DLQI and VAS pain scores were observed with adalimumab. Similar PASI 75 response rates were observed in patients with and without scalp involvement
Multiple TNF-α inhibitors						
Fotiadou et al. (2016)	Retrospective cohort study	Database review of patients with scalp psoriasis receiving biologic treatment	145	Infliximab (n = 35), etanercept (n = 30), adalimumab (n = 39), and ustekinumab (n = 41)	48 weeks	At week 4, patients receiving infliximab, ustekinumab, etanercept, and adalimumab achieved mean decreases in PSSI of 74%, 62%, 53% and 54%, respectively. At week 48 mean changes in PSSI were 94%, 95%, 83%, and 89%, respectively
Secukinumab (IL-17 inhibitor)						
Bagel et al., 2017	Randomized, double-blind, placebo-controlled trial	Prospective study of moderate-to-severe scalp psoriasis, with or without body plaque psoriasis	102	Secukinumab (300 mg) or placebo at baseline, weeks 1, 2 and 3 and then every 4 weeks from week 4	24 weeks	At week 12, secukinumab vs. placebo provided greater responses for PSSI 90 (53% vs. 2.0%), IGA mod 2011 scalp responses of 0 or 1 (57% vs. 6%), and PSSI 100 (35% vs. 0%; all $p < .001$). Responses were maintained to week 24

(Continues)

TABLE 1 (Continued)

Study	Study design	Primary location evaluated	Size, *n*	Treatment	Duration	Results/remarks
Ixekizumab (IL-17 inhibitor)						
Langley et al. (2015)	Randomized, double-blind, placebo-controlled trial	Subanalysis of phase 2 trial that evaluated scalp psoriasis in patients with moderate-to-severe psoriasis	105	Ixekizumab (10 mg, 25 mg, 75 mg, or 150 mg) or placebo at weeks 0, 2, 4, 8, 12, and 16 with an open-label extension of ixekizumab (120 mg) Q4W for 48 weeks	20 weeks with a 48-week open-label extension	At week 20, mean percent improvement from baseline PSSI of 75% for ixekizumab 25 mg, 84% for ixekizumab 75 mg, and 82% for ixekizumab 150 mg compared with 19% with placebo (all $p \leq .001$). At week 48, 78% of patients receiving ixekizumab achieved a PSSI score of 0
Reich et al. (2017)	Randomized, double-blind, placebo- and active-controlled trials	Subanalysis of 3 phase 3 trials that evaluated scalp psoriasis in patients with moderate-to-severe psoriasis	3524	Ixekizumab (80 mg) or placebo Q2W or Q4W after 160 mg starting dose or etanercept (50 mg) twice weekly	60 weeks	At week 12, PSSI 90 was achieved by 76%–82% of patients receiving ixekizumab, 56% receiving etanercept ($p<.001$), and 8% receiving placebo ($p<.001$) and PSSI 100 was achieved by 69%–75% of patients receiving ixekizumab, 48% receiving etanercept ($p<.001$), and 7% receiving placebo ($p<.001$). Responses were maintained to week 60
Apremilast (PDE4 inhibitor)						
Rich et al. (2016)	Randomized, double-blind, placebo-controlled trial	Subanalysis of 2 phase 3 trials that evaluated moderate-to-very severe scalp psoriasis in patients with moderate-to-severe psoriasis	832	Apremilast (30 mg) or placebo	52 weeks	At week 16, a ScPGA score of 0 or 1 was achieved by 41%–47% of patients receiving apremilast ($p<.0001$ vs. placebo for both studies)
Non-targeted agents						
Lebwohl et al. (2016)	Randomized, double-blind, 3-arm study	Whole body	302	Calcipotriene 0.005% (Cal) plus betamethasone dipropionate 0.064% (BD) aerosol foam; Cal aerosol foam; BD aerosol foam	4 weeks	At week 1, more patients treated with Cal/BD aerosol foam (26%) achieved scalp treatment success[b] compared with those treated with Cal aerosol foam (8%; $p<.001$) or BD aerosol foam (14%; $p=.016$). At week 4, more patients treated with Cal/BD aerosol foam (53%) achieved scalp treatment success[b] than with Cal aerosol foam (36%; $p=.021$), but not BD aerosol foam (48%; $p=.45$)
Facial						
Adalimumab (TNF-α inhibitor)						
Navarini et al. (2014) (CHAMPION)	Randomized, double-blind, placebo-controlled study	Subanalysis of phase 3 trial that evaluated PASI subcomponents	271	Adalimumab (80 mg at week 0, followed by 40 mg every other week for 15 weeks) or methotrexate (7.5 mg at weeks 0 and 1, 10 mg at weeks 2 and 3, and 15–25 mg until week 15)	16 weeks	More patients achieved PASI 75, 90, and 100 with adalimumab at week 16. Results include entire head (mean percent improvement in PASI at week 16: adalimumab, 81%; methotrexate, 57%; placebo, 27%)
Non-targeted agents						
Liao et al. (2007)	Randomized, double-blind, head-to-head comparison	Face or genitofemoral region	50	Calcitriol ointment (3 μg/g twice daily) or tacrolimus ointment (0.3 mg/g twice daily)	6 weeks	Tacrolimus was more effective based on TAS and PGA at week 6. Patients with genitofemoral psoriasis were included in results
Ortonne, Noerrelund, et al. (2010)	Randomized, double-blind, 4-arm parallel-group study	Face	408	Calcipotriol ointment (25 μg/g or 50 μg/g) alone or combined with hydrocortisone (10 μg/g) once daily	8 weeks	The combination of calcipotriol and hydrocortisone was more effective in reducing PASI scores than calcipotriol alone but no difference was found between calcipotriol concentrations

(Continues)

TABLE 1 (Continued)

Study	Study design	Primary location evaluated	Size, *n*	Treatment	Duration	Results/remarks
Jacobi et al. (2008)	Open-label investigator-initiated study	Face	20	Pimecrolimus 1% cream twice daily	16 weeks	Pimecrolimus reduced total symptom score, IGA, pruritus, patient's assessment score and DLQI after 8 and 16 weeks
Palmoplantar						
Infliximab (TNF-α inhibitor)						
Bissonnette et al. (2011)	Randomized, double-blind, placebo-controlled trial	Palms and soles	24	Infliximab (5 mg/kg) at weeks 0, 2, 6, and then every 8 weeks; placebo group received infliximab at weeks 14, 16, and 20	22 weeks	Primary endpoint of m-PPPASI 75 at week 14 not met (infliximab, 33% vs. placebo, 8%; $p=.317$). PPSA and m-PPPASI 50 were improved at week 14 with infliximab
Ustekinumab (IL-12/23 inhibitor)						
Au et al. (2013)	Open-label trial	Palms and soles	20	Ustekinumab (45 mg for patients <100 kg and 90 mg for patients ≥100 kg) at weeks 0, 4, and 16	16 weeks	At week 16, 35% of patients achieved a Palm-Sole PGA score ≤1 (67% of patients receiving ustekinumab 90 mg vs. 9% of patients receiving ustekinumab 45 mg; $p=.02$). An improvement of ≥2 on the Palm-Sole PGA scale was achieved by 60% of patients
Secukinumab (IL-17 inhibitor)						
Paul et al. (2014)	Randomized, double-blind, placebo-controlled	Subanalysis of phase 2 trial that evaluated palm and/or sole psoriasis in patients with moderate-to-severe psoriasis	131	Secukinumab (150 mg): single (week 0), monthly (weeks 0, 4, and 8), early (weeks 0, 1, 2, and 4); or placebo	12 weeks	At week 12, more patients receiving the early regimen of secukinumab achieved a hand/foot IGA response of 0/1 than patients receiving placebo (54% vs. 19%; $p=.005$)
Gottlieb et al. (2017)	Randomized, double-blind, placebo-controlled trial	Palms and soles	205	Secukinumab (300 mg or 150 mg) or placebo at baseline, weeks 1, 2 and 3 and then every 4 weeks from week 4	16 weeks	At week 16, ppIGA 0/1 was achieved by 33.3% of patients receiving secukinumab 300 mg and 22.1% of patients receiving secukinumab 150 mg compared with 1.5% of patients receiving placebo ($p<.001$ for both)
Ixekizumab (IL-17 inhibitor)						
Menter et al. (2017)	Randomized, double-blind, placebo- and active-controlled trials	Subanalysis of 3 phase 3 trials that evaluated palm and/or sole psoriasis in patients with moderate-to-severe psoriasis	350	Ixekizumab (80 mg) or placebo Q2W or Q4W after 160 mg starting dose or etanercept (50 mg) twice weekly	60 weeks	At week 12, PPPASI 75 was achieved by 70%–74% of patients receiving ixekizumab, 44% receiving etanercept, and 19% receiving placebo ($p<.05$ for all) and PPPASI 100 was achieved by 49%–52% of patients receiving ixekizumab, 32% receiving etanercept ($p<.05$), and 8% receiving placebo ($p<.001$). Responses were maintained to week 60
Apremilast (PDE4 inhibitor)						
Bissonnette et al. (2016)	A single randomized, placebo-controlled study and 2 randomized, double-blind, placebo-controlled studies	Subanalysis of 1 phase 2b trial (PSOR-005) and 2 phase 3 trials (ESTEEM 1 and 2) that evaluated palm and/or sole psoriasis in patients with moderate-to-severe psoriasis	427	Apremilast (30 mg), twice daily or placebo	16 weeks	At week 16, more patients receiving apremilast than placebo achieved a PPPGA score of 0 or 1 (48% vs. 27%; $p=.021$), and had a PPPGA score of 0 or 1 with a ≥1 point improvement (59% vs. 39%; $p<.001$)

(Continues)

TABLE 1 (Continued)

Study	Study design	Primary location evaluated	Size, *n*	Treatment	Duration	Results/remarks
Nontargeted agents						
Sezer, Erbil, Kurumlu, Taştan, and Etikan, (2007)	Randomized, within-patient, paired left-to-right comparison	Palms and soles	25	NB-UVB or PUVA 3 times a week	9 weeks	PUVA was more effective than NB-UVB in reducing severity index scores
Mehta and Amladi (2011)	Observer-blinded, randomized controlled study	Palms and soles	30	Tazarotene cream (0.1%), once daily or clobetasol propionate cream (0.05%), once daily for 12 weeks	12 weeks	At week 12, patients receiving tazarotene or clobetasol achieved an 83.2% and 89.1% mean ESFI reduction, respectively, and 52.9% and 61.5% of patients achieved complete clearance, respectively
Janagond et al. (2013)	Randomized, head-to-head comparison	Palms and soles	111	Methotrexate (0.4 mg/kg weekly) or acitretin (0.5 mg/kg daily)	12 weeks	Methotrexate had a greater m-PPPASI response at weeks 8 and 12 ($p<.05$) without increasing adverse events
Nail						
Etanercept (TNF-α inhibitor)						
Ortonne et al. (2013)	Randomized, head-to-head comparison	Nails	69	Etanercept (50 mg) twice weekly for 12 weeks followed by once weekly for 12 weeks, or etanercept (50 mg) once weekly for 24 weeks	24 weeks	Both doses of etanercept showed improved NAPSI scores at weeks 12 and 24
Adalimumab (TNF-α inhibitor)						
Paul et al. (2012)	Randomized, double-blind, vehicle-controlled trial	Subanalysis of phase 3 trial that evaluated nail psoriasis in patients with and without psoriatic arthritis	730	Adalimumab (80 mg) at week 0 and adalimumab (40 mg) every other week for 15 weeks with or without calcipotriol/betamethasone dipropionate (nails excluded)	16 weeks	Adalimumab improved NAPSI, pruritus, and DLQI scores at week 16
Thaci et al. (2015)	Randomized, double-blind, vehicle-controlled trial	Subanalysis of phase 3 trial that evaluated nail psoriasis in a pooled treatment group (adalimumab with or without calcipotriol plus betamethasone dipropionate) of patients with moderate-to-severe psoriasis	457	Adalimumab (80 mg at week 0; followed by 40 mg every other week from weeks 1–15) in addition to either topical calcipotriol plus betamethasone dipropionate or drug-free vehicle applied once daily for 4 weeks, and as needed thereafter	16 weeks	At week 16, there was a median decrease from baseline NAPSI of 40% with adalimumab. Improvements in DLQI and VAS pain scores were observed with adalimumab. Lower PASI 75 response rates were observed in patients with nail involvement
Ustekinumab (IL-12/23 inhibitor)						
Rich et al. (2014)	Randomized, double-blind, placebo-controlled trial	Subanalysis of phase 3 trial that evaluated nail psoriasis	545	Ustekinumab (45 mg or 90 mg) at weeks 0, 4, 16, and 28; placebo group received ustekinumab at weeks 12, 16, and 28	52 weeks	Both doses of ustekinumab showed improved NAPSI scores at weeks 12 and 24
Secukinumab (IL-17 inhibitor)						
Paul et al. (2014)	Randomized, double-blind, placebo-controlled trial	Subanalysis of phase 2 trial that evaluated nail psoriasis in patients with moderate-to-severe psoriasis	304	Secukinumab (150 mg): single (week 0), monthly (weeks 0, 4, and 8), early (weeks 0, 1, 2, and 4); or placebo	12 weeks	Percentage mean change from baseline to week 12 in composite nail score of −19% with the early regimen of secukinumab ($p=.010$ vs. placebo) and −11% with the monthly regimen of secukinumab ($p=.027$ vs. placebo)

(Continues)

TABLE 1 (Continued)

Study	Study design	Primary location evaluated	Size, *n*	Treatment	Duration	Results/remarks
Ixekizumab (IL-17 inhibitor)						
Langley et al. (2015)	Randomized, double-blind, placebo-controlled trial	Subanalysis of phase 2 trial that evaluated nail psoriasis in patients with moderate-to-severe psoriasis	58	Ixekizumab (10 mg, 25 mg, 75 mg, or 150 mg) or placebo at weeks 0, 2, 4, 8, 12, and 16 with an open-label extension of ixekizumab (120 mg) Q4W for 48 weeks	20 weeks with a 48-week open-label extension	At week 20, significant improvement in mean percent improvement from baseline NAPSI was observed with ixekizumab 75 mg (64%; $p=.003$) and ixekizumab 150 mg (53%; $p=.009$) compared with placebo (2%). At week 48 of the open label extension, 51% of patients receiving ixekizumab achieved a NAPSI score of 0
van de Kerkhof et al. (2017)	Randomized, double-blind, placebo- and active-controlled trials	Subanalysis of phase 3 trial that evaluated nail psoriasis in patients with moderate-to-severe psoriasis	809	Ixekizumab (80 mg) or placebo Q2W or Q4W after 160 mg starting dose or etanercept (50 mg) twice weekly	60 weeks	At week 12, mean percent improvement in NAPSI of 37% with ixekizumab Q4W and 35% with ixekizumab Q2W compared to −34% for placebo ($p<.001$ for both) and 20% for etanercept ($p=.048$ for ixekizumab Q4W, and $p=.072$ for ixekizumab Q2W). Improvement continued to week 60 with ixekizumab
Apremilast (PDE4 inhibitor)						
Rich et al. (2016)	Randomized, double-blind, placebo-controlled trial	Subanalysis of 2 phase 3 trials that evaluated nail psoriasis in patients with moderate-to-severe psoriasis	824	Apremilast (30 mg) twice daily or placebo	52 weeks	At week 16, mean percent change in NAPSI of −23% ($p<.0001$ vs. placebo) and −29% ($p=.0052$ vs. placebo) with apremilast. At week 16, NAPSI 50 response rates of 33%–45% were achieved with apremilast ($p<.0001$ vs. placebo for both studies). NAPSI 50 response rates were generally maintained to week 52
Tofacitinib (Janus kinase inhibitor)						
Merola, Tatulych, et al. (2016)	Randomized, double-blind, placebo-controlled trial	Subanalysis of 2 phase 3 trials that evaluated nail psoriasis in patients with moderate-to-severe psoriasis	1196	Tofacitinib (5 mg or 10 mg) twice daily or placebo. At week 16, patients receiving placebo were re-randomized to tofacitinib 5 mg or tofacitinib 10 mg	52 weeks	At week 16, the mean percent change from baseline in NAPSI was greater with tofacitinib 5 mg (−17.4%) and tofacitinib 10 mg (−34.2%) than placebo (35.0%; both $p<.01$). The percentage of patients achieving NAPSI 75 at week 16 with tofacitinib 5 mg, tofacitinib 10 mg, and placebo were 16.9%, 28.1%, and 6.8%, respectively. At week 52, the mean reduction in NAPSI from baseline was −65.6% for tofacitinib 5 mg and −75.5% for tofacitinib 10 mg

Abbreviations: CHAMPION = Comparative Study of Humira versus Methotrexate versus Placebo in Psoriasis Patients; DLQI = Dermatology Life Quality Index; ESFI = Erythema, Scaling, Fissures and Induration; ESTEEM = Efficacy and Safety Trial Evaluating the Effects of Apremilast in Psoriasis; IGA = Investigator's Global Assessment; IGA mod 2011 = Investigator's Global Assessment modified 2011; m-PPPASI = modified Palmoplantar Psoriasis Area and Severity Index; NAPSI = Nail Psoriasis and Severity Index; NB-UVB = Narrowband Ultraviolet Phototherapy; PASI = Psoriasis Area and Severity Index; PDE4 = phosphodiesterase 4; PGA = Physician's Global Assessment; PPPASI = Palmoplantar Psoriasis Area and Severity Index; PPPGA = Palmoplantar Psoriasis Physician Global Assessment; ppIGA = palmoplantar Investigator's Global Assessment; PPSA = Palmoplantar Psoriasis Surface Area; PSSI = Psoriasis Scalp Severity Index; PUVA = Psoralen plus Ultraviolet A; Q2W = every 2 weeks; Q4W = every 4 weeks; ScPGA = Scalp Physician Global Assessment; TAS = Target Area Score; TNF = tumor necrosis factor; VAS = visual analog scale.

[a]Intertriginous and genital psoriasis are excluded from this table due to a lack of recent clinical trials.

[b]Treatment success was defined as PGA responses of "clear" or "almost clear" from baseline for patients with moderate/severe disease and "clear" from baseline for those with mild disease.

their durable medical equipment insurance to obtain them. Use of methotrexate and biologics is much needed in these patients. However, approval through payers can prove difficult as current on-label indications require significant body-surface-area coverage or a high-enough PASI score to qualify for these systemic agents.

2.2 | Facial

Facial psoriasis typically presents at a younger age and is estimated to affect nearly 50% of patients with psoriasis (Canpolat et al., 2008). Further, the presence of highly visible lesions can result in considerable psychosocial problems (Beattie & Lewis-Jones, 2006). The treatment of facial psoriasis is complicated by underappreciation of its prevalence despite being a marker of more severe disease (Canpolat et al., 2008). In patients with facial psoriasis, whole-body PASI scores are typically higher (15.6) than in patients without facial involvement (6.9), and they are also more likely to have a Koebner phenomenon (70.2% vs. 29.8%) (Canpolat et al., 2008). Additionally, psoriasis in this area is associated with longer disease duration, earlier onset, and frequently requires more extensive treatment, and it may sometimes be dismissed as seborrheic dermatitis or sebopsoriasis (Young Park, Hyun Rim, Beom Choe, & Il Youn, 2004).

Facial psoriasis is classified into 3 categories based on lesion distribution: mixed (39.1%), peripherofacial (37.1%), and centrofacial (23.7%) (van de Kerkhof et al., 2007). Centrofacial involvement likely indicates patients with the most severe form of facial psoriasis because it is associated with higher mean total-body PASI scores, a lower age of onset, and requires more extensive treatment than the peripherofacial variant (Woo, Choi, Yoon, Jo, & Youn, 2008). Patients with mixed type had significantly higher facial, scalp, and total-body PASI scores than the other 2 forms (Woo et al., 2008). Patients with facial involvement are more likely to report nail involvement, pruritus, symptoms that worsen with trauma, and hospitalization due to psoriasis (Young Park et al., 2004).

In recent years, research on facial psoriasis was limited to a small number of trials, and systemic therapy has been investigated in only a single study (Table 1). For topical therapies, the immunomodulatory calcineurin inhibitor, tacrolimus, was more effective than calcitriol, whereas calcipotriol combined with hydrocortisone showed greater clearance than calcipotriol alone (Liao, Chiu, Tseng, & Tsai, 2007; Ortonne, Noerrelund, et al., 2010). Topical pimecrolimus is also effective in treating facial psoriasis (Jacobi, Braeutigam, Mahler, Schultz, & Hertl, 2008). In 1 post hoc analysis, systemic therapy with adalimumab was more efficacious than methotrexate and placebo (Navarini, Poulin, Menter, Gu, & Teixeira, 2014).

In the short term, treatment can consist of milder topical steroids, but these agents present the risk of provoking acne, atrophy, and ocular side effects. Topical vitamin D analogs and pimecrolimus are effective steroid-sparing agents. For milder disease on the seborrheic dermatitis spectrum, ketoconazole 2% cream may be helpful.

2.3 | Intertriginous (inverse)

Inverse psoriasis typically presents as smooth, well-demarcated, inflamed areas, with little-to-no scaling and possible superficial erosion and maceration. These lesions result in intense itching, irritation from sweating, and soreness. Traditionally, inverse psoriasis was thought to be uncommon, but recent findings place the prevalence at 21–30% of patients with psoriasis (Merola, Li, et al., 2016). For patients with inverse psoriasis, the groin is the most commonly affected area and the external genitalia are involved in almost 80% of patients (Wang, Li, Gao, & Liu, 2005).

Treatment of inverse psoriasis must be approached with special care due to increased percutaneous absorption of steroids, phenols, and alcohols in the affected areas (Wozel, 2008). Thus, ideal treatment options should be odorless, cosmetically acceptable, chemically and physically stable, not irritating, and have no systemic absorption (Wozel, 2008). A review of treatment options for inverse psoriasis indicated that data were limited by a lack of clinical trials and the poor quality of published studies (Kalb et al., 2009). With the evidence available, low- to mid-potency topical steroids were identified as first-line options for short-term treatment and calcipotriol or pimecrolimus/tacrolimus for long-term therapy. However, calcipotriol can be irritating when used in skin folds (Kalb et al., 2009). QoL data focused on patients with inverse disease are limited, but it likely represents a substantial burden in interpersonal interactions (Cohen et al., 2016).

Severe inverse psoriasis resistant to topical treatment could necessitate the use of traditional oral systemic therapies, newer biologic therapies, or the phosphodiesterase 4 (PDE4) inhibitor, apremilast. Additionally, targeted excimer laser therapy can be used for patients with psoriasis in defined focal areas.

2.4 | Genital

Genital psoriasis is found in about 30–40% of patients with psoriasis and is more common in men (Meeuwis et al., 2010; Meeuwis, de Hullu, Massuger, van de Kerkhof, & van Rossum, 2011). Additionally, 63% of patients with psoriasis report ever having experienced genital psoriasis (Ryan et al., 2015). Not all cases of genital psoriasis fall under the inverse category, with some cases demonstrating plaque disease.

Over two-thirds of patients with genital psoriasis have never applied treatment to their genital lesions (Meeuwis, van de Kerkhof, Massuger, de Hullu, & van Rossum, 2012). Such undertreatment is likely due, at least in part, to patients not receiving options for managing the condition because 45% of patients who discussed genital lesions with their physician reported not receiving treatment (Meeuwis, de Hullu, van de Nieuwenhof et al., 2011). Genital psoriasis has a significant negative effect on QoL and sexual health (Meeuwis, de Hullu, van de Nieuwenhof et al., 2011; Ryan et al., 2015).

In a systematic literature review, only 7 studies on the treatment of genital psoriasis were identified, and these primarily consisted of case reports (Meeuwis, de Hullu, Massuger, et al., 2011). Based on these limited results, low-potency topical corticosteroids were identified as first-line therapy followed by vitamin D preparations or tar-based treatments. Pimecrolimus cream may be beneficial when used to treat the glans penis. Additionally, topical tacrolimus, another immunomodulator, has been identified as a treatment option for males with genital psoriasis (Bissonnette, Nigen, & Bolduc, 2008). Currently, a trial

to determine the efficacy of ixekizumab toward genital psoriasis is ongoing (ClinicalTrials.gov NCT02718898).

In clinical practice, intermittent flares of genital psoriasis are treated with low-potency topical steroids, vitamin D analogs, calcineurin inhibitors, retinoids, or retinoid analogs (e.g., tazarotene). As with inverse psoriasis, severe cases of genital psoriasis can be treated with traditional systemic therapies, newer biologic therapies, or apremilast; however, specific data are lacking for the efficacy of biologic and small-molecule inhibitors in genital psoriasis.

2.5 | Hands and feet (palmoplantar)

Palmoplantar psoriasis occurs in 12–16% of patients with psoriasis (Merola, Li, et al., 2016). The morphology can vary from predominately pustular lesions to thick hyperkeratotic plaques (Farley, Masrour, McKey, & Menter, 2009). Other dermatoses such as palmoplantar pustulosis and dermatitis repens (also known as acrodermatitis continua of Hallopeau) are generally included in the spectrum of disorders classified as palmoplantar psoriasis (Brunasso et al., 2013; Farley et al., 2009).

Although involvement of the palms and soles often affects < 5% of total body surface area (and, consequently, may be characterized as mild disease when measured by PASI score), these patients may suffer from greater physical limitations than individuals with psoriasis in other areas (Farley et al., 2009; Pettey, Balkrishnan, Rapp, Fleischer, & Feldman, 2003). Patients with palmoplantar psoriasis reported greater functional disability, burning, soreness, and health-related QoL impairment than patients with other forms of psoriasis, with 34% of patients being severely affected by their condition, 48% being moderately affected, and only 18% being mildly affected (Chung et al., 2014; Farley et al., 2009; Pettey et al., 2003).

Treatment goals for palmoplantar psoriasis may differ from other forms of the disease, as considerable treatment satisfaction can be obtained by alleviating pain and discomfort (Pettey et al., 2003). Methotrexate significantly improved modified palmoplantar psoriasis area and severity index (m-PPPASI) scores relative to the retinoid acitretin (Table 1) (Janagond, Kanwar, & Handa, 2013). Additionally, ustekinumab, secukinumab, and apremilast significantly improved palmoplantar psoriasis compared with placebo; and ixekizumab provided significant improvement compared to etanercept and placebo (Au et al., 2013; Bissonnette et al., 2016; Gottlieb et al., 2017; Menter et al., 2017; Paul et al., 2014). However, infliximab failed to meet a primary endpoint of m-PPPASI 75 at week 14 compared with placebo (Bissonnette et al., 2011).

The strategy for treatment of palmoplantar psoriasis varies based on the presence of pustular psoriasis. In the absence of pustular psoriasis, potent topical steroids, hand and foot ultraviolet therapy, bath psoralen plus ultraviolet A, tar-based soaps (liquor carbonis detergens), and compounded products (e.g., keratolytic with a potent steroid) are all considered effective treatment options. Vitamin D analogs may be prescribed, but are less effective in thick-skinned areas such as the hands and feet. More severe cases of palmoplantar psoriasis may require traditional systemic treatments such as methotrexate or acitretin, or newer biologic therapies such as secukinumab. The PDE4 inhibitor, apremilast is also efficacious toward palmoplantar psoriasis (Bissonnette et al., 2016). In addition to these treatment options, recalcitrant cases of pustular palmoplantar psoriasis can be treated with oral or topical dapsone (Sheu, Divito, Enamandram, & Merola, 2016).

2.6 | Nail

Nail involvement is found in 23–27% of patients with psoriasis (Merola, Li, et al., 2016). The most common symptoms are pitting and onycholysis with subungual hyperkeratosis, nail-bed discoloration, nail-plate abnormalities, and, less frequently, splinter hemorrhages (Baran, 2010). Nail psoriasis is associated with significant pain and physical impairment (including from psoriatic arthritis, which may be more common with nail involvement), as well as issues such as: self-image and cosmetic concerns, difficulty with tasks involving manual dexterity, anxiety and/or depression, an increased number of missed work days relative to patients without nail involvement, and substantial impairments in QoL (Augustin et al., 2010; Klaassen, van de Kerkhof, & Pasch, 2014; Langley, Saurat, Reich, & Nail Psoriasis Delphi Expert Panel, 2012; Ortonne, Baran, et al., 2010).

A systematic review evaluating treatments for nails psoriasis found the quality of published studies was generally poor (de Vries et al., 2013). However, the anti-tumor necrosis factor monoclonal antibodies infliximab and golimumab, superficial radiotherapy, Grenz rays, and electron beam therapy were effective in comparative placebo-controlled studies. Systemic therapies were recommended only for individuals who required them for other psoriatic conditions, had severe nail psoriasis, were recalcitrant to other therapy, or had reduced QoL (de Vries et al., 2013). Another option for nail psoriasis is intralesional steroid-injection therapy, which is limited by the pain of injection; however, recent data from a small ($N = 17$) prospective trial suggested high efficacy for novel administration via needle-free jet injector (Nantel-Battista, Richer, Marcil, & Benohanian, 2014). Laser therapy can also be considered for patients with nail psoriasis and in a single blinded left-to-right comparison study ($N = 42$), treatment with pulsed-dye laser was significantly more effective than excimer laser (Al-Mutairi, Noor, & Al-Haddad, 2014). Additionally, the efficacies of pulsed-dye laser and neodymium-doped yttrium aluminum garnet (Nd:YAG) laser are comparable, but Nd:YAG laser therapy is more painful (Arango-Duque, Roncero-Riesco, Usero Bárcena, Palacios Álvarez, & Fernández López, 2017). Psoralen plus ultraviolet A is not recommended for nail psoriasis because only a minimal amount of ultraviolet type-A light penetrates the nail (Stern, Creasey, Quijije, & Lebwohl, 2011).

Targeted, systemic treatment with adalimumab, etanercept, ixekizumab, secukinumab, ustekinumab, tofacitinib, and apremilast effectively improved symptoms of nail psoriasis (Table 1) (Langley et al., 2015; Merola, Tatulych, et al., 2016; Ortonne et al., 2013; Paul et al., 2012, 2014; Rich et al., 2014, 2016; Thaci et al., 2015; van de Kerkhof et al., 2017). Results suggest that these patients could benefit from new agents that produce high levels of clearance in shorter periods. In 2015, the National Psoriasis Foundation issued the following best practice recommendations for the treatment of nail psoriasis (Crowley, Weinberg, Wu, Robertson, & Van Voorhees, 2015). For patients with

psoriasis limited to the nails, high-potency topical corticosteroids alone or in combination with calcipotriol were highly recommended, and intralesional corticosteroids can be considered. For patients with psoriasis limited to the nails who had failed topical therapy, the following therapies were recommended in order of preference: adalimumab, etanercept, intralesional corticosteroids, ustekinumab, methotrexate, and acitretin (Crowley et al., 2015). Although biologics are the most effective option for nail psoriasis, their price can limit their use (Demirsoy et al., 2013).

Nail psoriasis can be challenging to treat. Frequently, patients will first be treated with topical steroids, but this is often not sufficient. Intralesional corticosteroids are effective, but painful. Radiotherapy, although not frequently employed, can be used for nonresponsive nails. In cases of severe nail psoriasis, systemic treatments—of which biologics are most effective—can be used.

3 | DISCUSSION

It is important for physicians to consider the debilitating nature of psoriasis of the scalp, face, nails, genitals, intertriginous, and palmoplantar regions when evaluating treatment strategies. The initial diagnosis of psoriasis in these regions may be more complicated because (a) physicians may not appreciate the full burden of disease in these areas and/or (b) patients may be reluctant to discuss disease affecting these areas unless specifically asked.

Another challenge stems from the inability of commonly used scoring systems to comprehensively detect disease severity in these regions due to the small surface area affected. Further, traditional scoring systems do not measure the impact of disease on a patient's emotional and physical well-being. New scoring systems that consider QoL measures in addition to the severity of psoriatic lesions can provide better guidance for determining the level of care required. For example, the Brigham Scalp Nail Inverse Palmoplantar Psoriasis Composite Index is comprised of patient-derived/patient-reported outcomes equally weighted with physician-assessed disease activity index scores to determine overall disease severity (Patel, Liu, Qureshi, & Merola, 2014).

Patient concerns and therapy limitations cause many commonly used agents to not be acceptable for treatment of psoriasis affecting the scalp, face, flexural/intertriginous, and palmoplantar regions (Table 2). The application of topical agents can be challenging and not cosmetically tolerable to many patients. Further, traditional systemic therapies may require different drug concentrations to be effective at the afflicted areas; thus, toxicity can be a major concern. Also, treatment may be further complicated by lack of response due to nonadherence because of difficulty in maintaining application schedules or other reasons. In addition, treatment selection is hampered by a lack of robust clinical trial data for psoriasis in these areas (Table 1). To determine the best treatment strategies, future trials may consider including individuals with psoriasis only in challenging-to-treat areas and incorporate QoL measures.

Recent advances in systemic treatments may benefit patients for whom topical approaches pose challenges. Through a more targeted approach directed at the underlying pathophysiology of lesion formation, new agents may offer greater efficacy in managing psoriasis of the head, flexures, and extremities, especially compared with traditional systemic agents that have limited distribution to certain areas. The development of biologic agents that target cytokines downstream of tumor necrosis factor-α could produce more rapid and more complete clearing of psoriatic lesions than current therapies. The implication of IL-17 in the pathogenesis of psoriasis has led to the development of new therapeutics aimed at IL-17 blockade, and these agents (e.g., secukinumab, ixekizumab) have strong efficacy and good safety in late-phase clinical trials for moderate-to-severe plaque psoriasis (Langley et al., 2014; Leonardi et al., 2012; Martin et al., 2013; Papp et al., 2012). Additionally, the expression of IL-17A is increased in the palms and soles of patients with palmoplantar pustular psoriasis, and targeting of IL-17A with secukinumab is efficacious in patients with moderate-to-severe palmoplantar psoriasis (Bissonnette et al., 2014; Gottlieb et al., 2017). In contrast, targeting IL-12/23 has limited efficacy in palmoplantar psoriasis (Bissonnette et al., 2014). Secukinumab also significantly improved moderate-to-severe scalp psoriasis in a prospective phase 3b trial (Bagel et al., 2017). Results are awaited from a prospective phase 3 trial of secukinumab in nail psoriasis (ClinicalTrials.gov NCT01807520; ClinicalTrials.gov NCT02267135).

Although additional data are necessary to determine the role of agents targeting IL-17 for routine management of psoriasis in other areas and nonplaque subsets, they may offer improved care and outcomes for patients whose needs are not met by available therapies.

TABLE 2 Considerations for the treatment of psoriasis by body region

Scalp	
	Topical therapies can be difficult to apply directly to the scalp
	Topical therapies can make the appearance of a patient's hair unacceptable
	External ultraviolet therapy does not penetrate well into the scalp
Facial	
	Topical therapies may not be cosmetically acceptable to the patient
	Delicate skin area particularly susceptible to steroid atrophy, steroid-induced acne
	Incomplete clearance is particularly unacceptable to patients (partial treatment)
Intertriginous (including genital)	
	Increased percutaneous drug absorption alters efficacy and safety profile (including risk of steroid atrophy)
	Often mistaken for candidal/fungal infection, delaying diagnosis and treatment
	Often not brought up by the patient or inquired about by the physician due to embarrassment or lack of awareness
Palmoplantar	
	Treatment goals should focus on alleviating pain and function as well as cosmetic improvement
	Has many functional, social, and occupational implications for the patient
Nail	
	Achieving effective drug concentrations is difficult with topical therapies
	Slow nail growth can make therapy response hard to assess
	Can be difficult to distinguish from concurrent fungal infection

Raising the awareness of psoriasis on the scalp, face, intertriginous areas, genitals, hands, feet, and nails is critical for comprehensive assessment of psoriasis. Currently, more targeted systemic therapies are available for psoriasis than in the past, and use of drugs discussed in this manuscript is important for improving clinical outcomes of all patients, regardless of affected body region. We recommend addressing the current gap in comprehensive psoriasis management through the development of better measurement tools that include all psoriasis phenotypes and incorporate the patient perspective as patient-reported outcomes, so that clinical trials can be conducted using these new psoriasis indices.

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CONFLICT OF INTEREST

Dr. Merola has served as an investigator for Amgen, Pfizer, and Biogen IDEC; has consulted for Biogen IDEC, Amgen, Eli Lilly, Janssen and Novartis; has served as a speaker for AbbVie. Dr. Qureshi has consulted for AbbVie, Celgene, Novartis, and Eli Lilly. Dr. Husni has consulted for AbbVie, Bristol-Myers Squibb, Pfizer, Celgene, Novartis, Eli Lilly, and Genentech.

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