

Psoriasis, Depression, and Suicidality

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Conflicts of interest: MJG has been an investigator, speaker or received honoraria from Amgen, AbbVie, Boehringer Ingelheim, Celgene, Dermira, Eli Lilly, Galderma, Janssen, Kyowa Kirin, Novartis, Pfizer, UCB, Valeant. MNN has no conflicts to disclose.

ABSTRACT

Psoriasis is a chronic condition that affects the well-being and quality of life of patients. The disease is associated with an increased risk of depression and suicidality, which may not be fully understood by the general population. It is crucial to understand the effect this disease has on mental health and determine risk factors that may help identify patients who are susceptible to depression and suicidality. Risk factors discussed in this article include age, gender, and severity of disease in psoriasis patients. Of these, age and severity of disease are significant with a clear association of increased depression and suicidality found in patients who are younger or have more severe disease. Although there is evidence that psoriasis treatments can improve both disease and associated depression symptoms, there are high rates of undertreatment. By identifying high-risk psoriasis patients, dermatologists can aim for optimal treatment of the disease and thus help alleviate the associated psychiatric burden.

Key words: psoriasis, depression, suicide, mental health, quality of life, risk factors

Introduction

Psoriasis is a chronic condition that often requires life-long treatment. It has been estimated that the disease affects approximately 1-3% of the population.¹ Psoriasis predominantly affects the skin as well as joints, with an incidence of almost 3% of psoriasis patients developing psoriatic arthritis annually, and reports of up to 42% of patients with psoriasis having associated psoriatic arthritis.^{2,3} Additionally, the increased risk for metabolic comorbidities such as obesity, diabetes, and cardiovascular events has also been demonstrated among patients with psoriasis.^{4,5}

Aside from the physical manifestation of symptoms, psoriasis is also linked to psychiatric disease. In a prospective cohort study looking at 50,750 female nurses in the US, those with psoriasis had an increased risk of depression compared to those without psoriasis, even when adjusted for potential confounders (relative risk [RR] 1.29 {95% confidence interval [CI] 1.10-1.52}). This RR was statistically similar when patients had both psoriasis and concomitant psoriatic arthritis (RR 1.52 [95% CI 1.06-2.19]).⁶ A number of other studies further support the increased risk in depression as shown by the meta-analysis and systematic review by Dowlatshahi et al. (2014).⁷ Although many skin conditions are associated with an increased risk of depression, psoriasis is one of few dermatological diseases that also increases suicidality risk of affected individuals. A study looking at different skin diseases across 13 European countries aimed to determine the association

between various dermatological diagnoses and depression and suicidal ideation. Although psoriasis was ranked fourth highest in increased incidence of depression (odds ratio [OR] 3.02 [95% CI 1.86-4.90]), it was the only skin disease associated with an increased incidence of suicidal ideation (OR 1.94 [95% CI 1.33-2.82]).⁸ One study reported an incidence of suicidal ideation in the previous 2 weeks as high as 10% in patients with psoriasis.⁹ This level of suicidal ideation translates into a clear risk for self-harm as reported by a retrospective European study that showed an increased RR for self-harm in 1,141 patients with psoriasis (RR 1.6 [95% CI 1.5-1.7]) compared to healthy controls.¹⁰

The reasons for this widened risk are multifold, relating to both biological changes and negative effects on self-image and quality of life. Cytokines involved in the inflammatory pathways of psoriasis can also lead to depression. For example, giving patients interferon for treatment of hepatitis C can induce and exacerbate their psoriasis while also commonly cause depression as a side effect.^{11,12} There are additional reports of improvement in mood when certain agents, such as tumor necrosis factor (TNF) inhibitors^{13,14} or an interleukin-12 and 23 inhibitor¹⁵, are given to treat psoriasis. Aside from biological changes, the appearance and discomfort of psoriatic lesions negatively impact both self-image and quality of life.^{16,17} Patients with psoriatic lesions on noticeable areas may attempt to cover themselves with additional clothing layers, experience difficulties with sexual function, and avoid

physical exercise.¹⁶ Patients report having persistent feelings of shame, worry, and frustration, which in turn affects work and hobby performance.¹⁸ The biological changes and decreased self-image and quality of life can lead to clinical diagnoses of depression, among other psychiatric disorders, as well as instances of suicidality. Although these diagnoses can be hard to predict, patients with psoriasis show increased prevalence of alexithymia, the inability to identify or describe their emotions.¹⁹ This can lead to depression and suicidality being underestimated, with many studies showing discordance between skin lesion severity and levels of distress.²⁰⁻²⁴ The distress that patients feel over their psoriasis can impair the efficacy of their treatments,²⁵ which may lead to a vicious cycle of distress, creating suboptimal clinical outcomes that in turn create further distress. Therefore, identifying patients most at risk for depression and suicidality may help to not only treat these psychiatric disorders, but also improve overall treatment of their psoriasis.

Risk Factors

Age

Psoriasis has a bimodal age of onset with the first presentation occurring in patients ranging from 15-20 years and the second presentation manifesting at 55-60 years.²⁶ In a descriptive cross-sectional study of 101 psoriasis patients, those who presented with psoriasis at less than 20 years of age had an increased incidence of depression compared to patients who presented at age 20 years or older.²⁷

Young age is also a risk factor for suicidality. A large population-based cohort study compared 766,950 patients without psoriasis to 149,998 patients with psoriasis; young patients demonstrated a higher risk for suicidality, defined here as one or more of suicidal ideation, suicide attempts or completed suicide.²⁸

Gender

There is substantial contradictory evidence on the effects of gender on psoriasis and psychiatric disease. One US study of randomly selected psoriasis patients used the Psoriasis Disability Index (PDI) to evaluate the effect of psoriasis on quality of life. Fifteen questions were asked regarding daily activities, leisure activities, relationships, work, and treatment, and one global question was asked regarding the effect of psoriasis on daily life. All questions were scored numerically with larger scores equating to a greater detrimental effect on quality of life. Younger patients had the highest disease burden on their quality of life, and females reported a greater PDI score than males.²⁹ However, in another

study of 6,497 Nordic patients, both genders reported similar PDI scores.³⁰ It is worth mentioning that males had a higher Psoriasis Area and Severity Index (PASI) score, suggesting they may be less likely to report decreased quality of life, even with worse disease as evidenced by their higher PASI score.³⁰

Multiple studies have failed to show an association between gender and depression rates in psoriatic patients. A case-control study carried out in Brazil looked at 100 patients with psoriasis and compared them to 100 healthy controls using the Beck Depression Inventory (BDI) to assess rates of depression between the two groups. The BDI is a validated set of 21 questions, each scoring in severity from 0-3 and targeting many different depression symptoms. In this study, a score of 17 or higher was deemed as possible clinical depression and the patient was referred to a psychiatrist for further confirmation. Women with psoriasis were slightly more depressed than their male counterparts as defined by the BDI, although this did not reach statistical significance.³¹ In a much larger study, overall there was no statistically significant difference between genders; however, in the severe psoriasis subgroup, there was a statistically significant increased rate of depression in male over female patients.²⁸

A relationship between gender and suicidality is not well supported. In the general population, the evidence has shown that females are at higher risk for suicide attempts, but completed suicide is more common in men.^{32,33} This is most likely related to the use of more lethal suicide methods in males.³⁴ In patients with psoriasis, two studies found no significant effect of patient gender on suicidal ideation or suicidality.^{28,35} Although suicidality is more prevalent in psoriasis patients, it does not appear to differ between males and females in this population.

Severity of Disease

The severity of psoriasis has a significant impact on the wellbeing of affected individuals. The burden of overall medical comorbidities increases with disease severity in the psoriatic population.³⁶ Severe psoriasis increases overall mortality, while mild psoriasis does not.³⁷ Although there may be discordance between severity of skin lesions and distress, severity of psoriasis may have some effect on rates of depression and suicidality.

In a comparison of 146,042 patients with mild psoriasis (treated only with topical therapy) and 3,956 patients with severe psoriasis (treated with systemic therapy) the adjusted RR of depression was increased with severe psoriasis when compared to mild psoriasis (hazard ratio [HR] 1.72 [95% CI 1.57-1.88]).²⁸ There was no

	Depression				Suicidality			
	Psoriasis Overall	Age	Gender	Psoriasis Severity	Psoriasis Overall	Age	Gender	Psoriasis Severity
Association	Increased compared to controls 6,8,28,31,38-41	Increased risk for younger patients 28	No significant difference* 28,31	Increased risk for severe disease 28	Increased compared to controls 8,10,28	Increased risk for younger patients 10,28	No significant difference 10,28	Increased risk for severe disease 28,38

Table 1. Associations found in psoriasis patients with depression and suicidality.

*Association found within subgroup of severe psoriasis patients with HR 1.21 (1.00-1.46) for male patients compared to female patients.²⁸

relationship between severity of disease and suicidality. Egeberg et al. (2016) reported increased suicidality with increased severity of disease by further subcategorizing areas of suicidality into different outcomes. This population-based cohort study looked at 408,663 Danish patients: 57,502 and 11,009 of these patients had mild and severe psoriasis, respectively. Although the study did not explore rates of depression, it did investigate suicidality by looking at incidences of self-harm or non-fatal suicide attempts, and fatal suicide attempts. Mild psoriasis showed no increased risk for either of the two outcomes, however severe psoriasis showed a slight increased risk in self-harm or non-fatal suicidal attempts (incidence rate ratio [IRR] 1.6 {95% CI 1.00-2.84}), but no increased risk of fatal suicidal attempt. This increased risk in self-harm or non-fatal suicide attempts was no longer significant when adjusted for concomitant psoriatic arthritis.³⁸

Undertreatment

Although a number of treatments exist for psoriasis, there is significant undertreatment of this disease. A study of 1,657 survey respondents identified from a random sample of the US National Psoriasis Foundation contact database showed that approximately 40% of patients with all severities of psoriasis were not receiving treatment. Additionally, 39% of patients with severe psoriasis were not receiving treatment and 35% were only being treated with topical therapies.⁴² Another study surveyed 391 dermatologists across North America and Europe in the Multinational Assessment of Psoriasis and Psoriatic Arthritis. Findings showed 92.1% of dermatologists agreed that the disease burden of psoriasis is largely underestimated; however, 53.5% of dermatologists stated they would treat moderate-to-severe psoriasis with topical therapies alone.⁴³

Successful treatment of psoriasis is helpful in decreasing rates of depression and suicidality in patients. A study looking at psychiatric morbidity in 414 patients with psoriasis used the General Health Questionnaire to identify individuals with psychological problems, defined as “cases,” and then repeated the same question in follow-up a month later. Sixty-eight percent of patients with complete clearing of psoriasis were deemed “noncases” at follow-up compared to 17.6% of patients with psoriasis whose condition was unchanged or worsened. Additionally, 70% of patients who had a $\geq 50\%$ improvement of psoriasis symptoms were deemed “noncases” compared to only 32% of patients with no improvement or worsening of psoriasis symptoms who were deemed “noncases” in follow-up.⁴⁴ Therefore, it is important to optimally treat psoriasis in order to alleviate the psychological burden. The use of more potent therapies, such as biologics, may be critical for targeting depressive symptoms. Depressive symptoms have been shown to improve in double-blinded randomized control trials of adalimumab¹³, etanercept¹⁴, and ustekinumab¹⁵.

Episodes of depression and suicide have recently become of interest when the clinical developmental program of an IL-17 receptor targeted biologic, brodalumab, was stopped due to reported cases of suicidality.⁴⁵ A causal link between brodalumab treatment and increased risk of suicidal ideation has not been established, and the drug was recently granted US FDA approval with a boxed warning of an observed risk. Nonetheless, current literature strongly supports the use of biologics, including those

targeting the IL-17 pathway, to improve both depression and suicidality in patients with psoriasis, and the reason for reported cases of suicidality is more likely due to the disease itself rather than any treatments used.⁴⁶

Screening

The dermatology office is often a busy place and, therefore, quick and easy screening tools are necessary if we hope to add depression screening to our clinical repertoire for managing psoriatic patients. The Patient Health Questionnaire-2 (PHQ-2) is a validated measure that screens for depressed mood and anhedonia over the past 2 weeks.⁴⁷ It is simply the first two questions of the PHQ-9 questionnaire that includes the nine items of the Diagnostic and Statistical Manual of Mental Disorders 4th edition (DSM-IV) criteria.⁴⁷ A simple algorithm for depression screening in psoriasis patients has recently been proposed by Korman et al. (2015) using the PHQ-2 as an initial screening measure.⁴⁸ Increased awareness of the link between depression and psoriasis and the use of simple screening tools may improve our ability to detect this important comorbidity.

Conclusion

Patients with psoriasis are at increased risk for depression and suicide at rates that are not fully appreciated. Consequently, it is important to understand the impacts that psoriasis can have on quality of life, including physical and mental health. Appropriate risk-stratification may help to identify high-risk patients. These risk factors would include younger patients with severe disease presentations especially with concomitant psoriatic arthritis. Females may present with greater distress over their psoriasis than males, but both genders are at risk for depression and suicidality. Further research is needed to elucidate the mechanism by which psoriasis is linked with psychological symptoms, as well as validate screening tools for dermatologists to identify high-risk individuals. All things considered, the optimal management of psoriasis must avoid inadvertent undertreatment while understanding the potential adverse effects that the disease can have on both the physical and emotional well-being of patients.

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The Role of Skin Care in Optimizing Treatment of Acne and Rosacea

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Conflicts of interest: CZ has no conflicts to disclose.

ABSTRACT

A triad approach to the treatment of acne and rosacea has been recommended. This integrated management approach includes patient education, selection of therapeutic agents, and initiation of an appropriate skin care regime. Proper skin care in patients undergoing treatment of both acne and rosacea includes use of products formulated for sensitive skin that cleanse, moisturize and photoprotect the skin. Both acne and rosacea are associated with epidermal barrier dysfunction, which can be mitigated by suitable skin care practices. Appropriate skin care recommendations for patients with acne and rosacea will be discussed.

Key words: acne, emollients, rosacea, photoprotection, skin barrier dysfunction, sunscreen, topical, transepidermal water loss

Acne

Acne vulgaris is the most common skin disease seen in dermatology office practice. Optimal management includes, in addition to selection of an appropriate therapeutic regimen, patient education and integration of proper skin care. Providing instructions on skin care and cosmetics to female acne patients improves quality of life compared to patients to whom no instructions are given.¹

Acne is associated with impaired epidermal barrier function.² Decreased stratum corneum hydration and reduced free sphingosine and total ceramide, indicative of an impaired stratum corneum intercellular lipid membrane, has been demonstrated in patients with acne. Although sebum excretion is increased in acne patients, alteration in the lipid composition of acne skin may further impair barrier function. Moreover, medications used to treat acne can alter stratum corneum integrity and function. An increase in transepidermal water loss has been shown with use of benzoyl peroxide, likely due to damage to the stratum corneum.³ Treatment with topical retinoids results in enhanced desquamation, reducing stratum corneum thickness and function. Use of appropriate skin care products in patients being treated for acne has been shown to increase adherence to pharmacological treatment and improve treatment outcomes.⁴

Cleansing

Although the majority of acne patients believe that suboptimal skin care and dirt on the skin contribute to acne,⁵ there are little scientific data to guide our recommendations regarding cleansing of acne prone skin.

The optimal frequency of cleansing is unclear, but most dermatologists recommend twice daily washing with a mild cleanser. One small study of males with mild to moderate acne compared the effect of face washing with a gentle cleanser once, twice or four times daily on acne severity.⁶ Although no statistically significant differences were noted between the groups, significant improvement in both open comedones and total inflammatory lesions were seen in the group washing twice daily. Worsening of acne was observed in the study group who

washed once a day, whereas washing four times daily did not adversely affect acne severity.

Although more frequent facial cleansing may not aggravate acne, aggressive scrubbing of the involved areas should be avoided to prevent irritation and trauma to underlying comedones, leading to increased inflammation.

Moisturizing

As acne prone skin is associated with epidermal barrier dysfunction which can be aggravated by acne medications, regular use of an emollient is an important part of acne therapy. Use of a noncomedogenic and nonacnegenic moisturizer is typically recommended. However, due to difficulties in testing for both comedogenicity and acnegenicity, including variability in individual patient susceptibility to acne formation, ensuring that a product will not trigger acne in a particular patient can be difficult.⁷

Sun Protection

Sun protection should also be recommended to acne patients.⁸ A systemic review found no convincing evidence that natural sunlight improves acne, although such studies are inherently difficult to conduct.⁹ Several oral acne treatments, including doxycycline and isotretinoin, are potentially photosensitizing.¹⁰ The US Food and Drug Administration official labelling for medications containing benzoyl peroxide and topical retinoids advises sun avoidance,^{11,12} although no effect on ultraviolet B-induced erythema was shown with use of either benzoyl peroxide or adapalene in one study¹³. In addition to providing sun protection, the emollient component of the sunscreen may improve epidermal barrier function. Finally, sun protective measures may prevent or minimize postinflammatory hyperpigmentation, particularly in patients with higher skin types.¹⁴

Rosacea

As is the case with acne, proper skin care is an important component of the management of rosacea. A triad approach to rosacea care has been suggested, which includes treatment, patient education regarding triggers, and advice as to appropriate

skin care and cosmetics.¹⁵ In a questionnaire sent to over 7000 individuals registered in the Canadian Rosacea Awareness Program, respondents expressed a strong interest in receiving more information on skin care, makeup and psychological aspects of rosacea.¹⁶

The involved skin of rosacea has been shown to exhibit increased transepidermal water loss due to impaired epidermal barrier function.¹⁷ Rosacea prone skin is also hyper-reactive; cutaneous insult results in prolonged vasodilation, exhibited clinically as facial erythema. Furthermore, the presence of an impaired stratum corneum barrier increases the irritancy of skin care products by enhancing penetration into the skin. Hence, skin care practices that optimize barrier function should be recommended.

Cleansing

Although skin cleansing is an important component of general skin care, surfactants contained in skin cleansers can weaken epidermal barrier function by disrupting proteins and lipids in the stratum corneum.¹⁸ Given the fact that patients with rosacea have impaired barrier function and a higher susceptibility to irritants, including sodium lauryl sulphate, mild cleansing is important.

The type of surfactant in the cleanser as well as its hydrogen ion concentration (pH) are major factors contributing to the irritant potential of a cleanser.¹⁸ Mild cleansers include synthetic detergents (syndets) and lipid-free cleansers. Syndet liquid cleansers or bars contain synthetic detergents and less than 10% soap. They have a favorable pH (5.5-7) and provide effective cleansing with less irritation potential than true soaps. Lipid-free cleansers have a neutral or slightly acidic pH. They are effective cleansers that leave a moisturizing film on the skin but do not lather.

Studies have shown benefits of mild cleansing in patients with rosacea. In a 4-week randomized, double-blind study of 70 patients with moderate rosacea who were using metronidazole 1% gel, subjects were instructed to use either a soap bar or a mild syndet bar. Use of the syndet cleanser reduced dryness, burning, stinging and itching compared to use of the soap bar.¹⁹

In addition to recommending an appropriate cleanser, physicians should advise rosacea patients to wash with lukewarm water, as hot water causes vasodilation and increased facial erythema. Mechanical trauma to the skin should also be minimized, including avoidance of granular exfoliants.

Astringents and toners, which are typically applied after cleansing, should likewise be avoided, as they tend to increase erythema and remove desirable oil from the skin.

Moisturizing

Use of appropriate moisturizers has several potential benefits in the management of rosacea. As rosacea skin has been shown to have increased transepidermal water loss, use of an emollient may improve barrier function and reduce dryness. Improved barrier function may also lead to reduced skin sensitivity and improved tolerance of topical medications.²⁰

Regarding choice of emollient, those containing potential irritants such as urea, glycolic acid, lactic acid, menthol and camphor should be avoided. Although the barrier dysfunction associated with rosacea may potentially increase allergenicity of skin care

products, minimal data is available on the prevalence of contact allergy in rosacea patients.²¹ However, as fragrances can cause both irritant and allergic reactions, fragrance-free products should be recommended. Cream type moisturizers are generally preferred over thin lotions and gels.

Sun Protection

Daily sun protection is an important component of rosacea management. Sun exposure is a common trigger of acute flares of rosacea, and chronic photodamage may also contribute to the pathogenesis of rosacea.²² Acute ultraviolet light may aggravate rosacea by stimulating proinflammatory peptide production, reducing cutaneous antioxidant reserves, and increasing production of reactive oxygen species.²³ However, finding a well-tolerated sunscreen can be difficult for rosacea patients. Selecting a cream based product containing an inorganic ultraviolet light filter and a silicone derivative, such as dimethicone or cyclomethicone, may reduce the likelihood of irritation.

Conclusion

Optimal management of both acne and rosacea includes initiation of an appropriate skin care regimen. This entails providing patients with advice regarding appropriate cleansing, moisturizing, and photoprotecting of the affected areas. Providing recommendations regarding skin care has been shown to improve quality of life in female acne patients and to be an unmet need in patients with rosacea. Integration of appropriate skin care in this patient population will improve barrier dysfunction and tolerability of prescribed therapy, leading to improved adherence and better treatment outcomes.

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Name/Company	Approval Dates/Comments
Dupilumab for SC injection <i>Dupixent</i> ® Sanofi/Regeneron Pharmaceuticals	In March 2017, the US FDA approved dupilumab, the first biologic for treating adults with moderate-to-severe atopic dermatitis (AD) whose disease is not adequately controlled with topical prescription therapies, or when those therapies are not advisable. Dupilumab is a human monoclonal antibody that specifically inhibits overactive signaling of two key cytokines, interleukin (IL)-4 and IL-13, which are believed to play a pivotal role in driving the chronic underlying inflammation in AD. Dupixent® comes in a pre-filled syringe and can be self-administered as a subcutaneous injection every other week after an initial loading dose, and can be used with or without topical corticosteroids. Most common adverse reactions (≥1%) are injection site reactions, conjunctivitis, blepharitis, oral herpes, keratitis, eye pruritus, other herpes simplex virus infection, and dry eye.
Dupilumab for SC injection Sanofi/Regeneron Pharmaceuticals	The UK Medicines and Healthcare products Regulatory Agency (MHRA) issued a positive opinion in March 2017 for dupilumab in atopic dermatitis (AD) under the Early Access to Medicines Scheme (EAMS). The decision allows eligible patients to receive the treatment prior to the drug gaining marketing authorization in the EU. Under the early access scheme, patients must have severe AD and failed to respond to, be intolerant to, or be ineligible for other therapies.
Avelumab for IV injection <i>Bavencio</i> ® EMD Serono/ Merck KGaA	In March 2017, the FDA approved avelumab, a human anti-programmed cell death ligand-1 (PD-L1) antibody, for the treatment of adults and pediatric patients ≥12 years of age with metastatic Merkel cell carcinoma (mMCC), including those who have not received prior chemotherapy. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials. This marks the first FDA-approved treatment for mMCC.
Hyaluronic acid-based injectable dermal filler <i>Juvéderm</i> ® <i>Vollure™ XC</i> Allergan plc	The FDA approved this hyaluronic acid (HA) dermal filler in March 2017 for correction of moderate-to-severe facial wrinkles and folds, such as nasolabial folds, in adults >21 years of age. Formulated with the proprietary Vycross® technology, which blends different molecular weights of HA, the product provides a longer duration of effect. Data from a clinical study showed 59% of patients had an improvement for up to 18 months. Additionally, 82% of patients reported they were very satisfied at 6 months and 68% of patients at 18 months. The product is known as Juvéderm® Volift™ in Canada and Europe, with approvals gained in 2014 and 2013, respectively.
Adalimumab for SC injection <i>Humira</i> ® AbbVie	In March 2017, the FDA approved the inclusion of moderate-to-severe fingernail psoriasis data in the adalimumab (Humira®) prescribing information for patients with moderate-to-severe chronic plaque psoriasis. Adalimumab is now the first-and-only biologic treatment with Phase 3 data on fingernail psoriasis in its US prescribing information. The study demonstrated nearly half of adult patients achieved an assessment of clear or minimal with at least a two-grade improvement from baseline in signs and symptoms of fingernail psoriasis compared to 6.9% of placebo (p<0.001).
Biosimilar to adalimumab for SC injection <i>Amgevita</i> ™ Amgen Inc.	In March 2017, the European Commission (EC) granted marketing authorization for Amgevita™ in all available indications, including psoriatic arthritis, moderate-to-severe chronic plaque psoriasis, and moderate-to-severe hidradenitis suppurativa. This approval also includes certain pediatric inflammatory diseases, including severe chronic plaque psoriasis (≥4 years of age).