Monograph

Advances in Psoriasis

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Abstract

Information on plaque psoriasis (PP) and its treatment are increasing at an impressive rate. This monograph is a broad overview of the current epidemiology, pathophysiology, genetics, and comorbidities (physical and psychological) of plaque psoriasis (PP). Also included is an overview of the myriad of the treatment options presently available and their efficacies. Topical therapies such as emollients and moisturizers, corticosteroids, keratolytics, anthralin, vitamin D3 analogs, calcineurin inhibitors, and retinoids are reviewed. Also included in the topical therapies are compounded medications with ingredients such as anthralin, coal tar, corticosteroids, cyanocobalamin, cyclosporine, ketotifen, methotrexate, naltrexone, salicylic acid, tacrolimus, urea, and zinc pyrithione. Combinations of topical ingredients often increase efficacy, for example, topical corticosteroids compounded with salicylic acid may be valuable due to increased penetration by the salicylic acid of the corticosteroids thus improving efficacy. The oral therapies reviewed include; acitretin, apremilast, azathioprine, corticosteroids, cyclosporine, fumaric acid esters, hydroxyurea, methotrexate, mycophenolate mofetil, tacrolimus, and 6-thioguanine. The biologics reviewed are Adalimumab, Brodalumab, Certolizumab Pegol, Etanercept, Guselkumab, Infliximab, Ixekizumab, Secukinumab, and Ustekinumab. The non-pharmacologic treatments discussed include phototherapy, lifestyle changes (addressing diet and stress impact), nutritional

supplements (fish oil, zinc, vitamin D, vitamin B12, and selenium), and alternative therapies. The financial impact of biologics, their added above-label use cost and the increased cost of comorbidities of the disease are discussed. Pregnancy warnings are reviewed and examples of drugs causing increased risk are illustrated e.g., acitretin, methotrexate, and tazarotene all belong to pregnancy category X, in contrast with UVB which can be safely used in the treatment of a pregnant woman with psoriasis.

List of Abbreviations

AAD-American Academy of Dermatology; AEs-Adverse Events; AGEs-Advanced Glycation End Products; APC-Antigen-Presenting Cells; API-Active Pharmaceutical Ingredient; BSA-Body Surface Area; CD-Celiac Disease; DC-Dendritic Cells; DLQI - Dermatology Life Quality Index; FABP2-Fatty Acid-Binding Protein 2; GM-CSF-Granulocyte-Macrophage Colony Stimulating Factor; IBS-Irritable Bowel Syndrome; IL-Interleukin; IFN-α-Interferon Alpha; IFNγ-Interferon Gamma; IgA EMA -Anti-Endomysial Antibody; LDN-Low Dose Naltrexone; LPS-Lipopolysaccharides; LS-PGA-Lattice-System Physician's Global Assessment; mDCs-Myeloid Dendritic Cells; MS-Multiple Sclerosis; OGF-Opioid Growth Factor; QOL-Quality Of Life; PGA-Psoriasis Global Assessment; PASI-Psoriasis Area and Severity Index; PP-Plaque Psoriasis; PsA-Psoriatic Arthritis; SA-Salicylic Acid; TCIs-Topical Calcineurin Inhibitors; TEWL-Trans-Epidermal

Water Loss; TLR9-Toll-Like Receptor 9; TNF-α-Tumor Necrosis Factor; tTG-IgA-Tissue Transglutaminase Antibodies; VEGF-Vascular Endothelial Growth Factor; WHO-World Health Organization.

Introduction

Many aspects of psoriasis are discussed in this monograph in order to elucidate some of the vast current knowledge of this disease and its application to practice. This includes the epidemiology, pathophysiology, and genetics of the disease also an overview of the myriad of the treatment options available at the present time. Treatments discussed are: topical therapies (including compounded medications), oral therapies, biologics (including two that are newly released), phototherapy, lifestyle changes, nutritional supplements and alternative therapies. Also presented are the relevant comorbidities of Plaque Psoriasis (PP), and some of the financial aspects of treatment and the associated comorbidities of this disease.

Epidemiology

Psoriasis is a noncommunicable, painful, disfiguring, morbid, chronic disease where patients with severe psoriasis have a shortened life expectancy. The published overall prevalence of this condition varies between reports. Prevalence has generally considered to be 2–3% worldwide, higher in American and Canadian populations(4.6–4.7%)

than in African and Asian populations (0.4–0.7%)[1]. The incidence in the US almost doubled from 1970 to 2000 but the prevalence among adults did not changed significantly since the mid-2000s and it was estimated that 7.4 million US adults were affected in 2013 [2].

According to the World Health Organization (WHO), psoriasis affects people of all ages, in all countries, with reported prevalence of ranges between 0.09% and 11.43%, making it a serious global problem with at least 100 million individuals affected worldwide [3]. Interestingly the occurrence of psoriasis varies according to age and geographic region, being more frequent in countries more distant from the equator [4].

Pathophysiology

There are many forms of psoriasis and the most common are plaque psoriasis (PP). PP is a complex chronic T-cell-mediated skin disease characterized by inflammation, hyper-proliferation, and abnormal differentiation of keratinocytes that often follows a relapsing and remitting course.Physical manifestations of psoriasis include the presence of raised, well-demarcated, scaly, erythematous oval plaque eruptions. Histological presentation includes the retention of keratinocyte nuclei in the stratum corneum (parakeratosis), thickening of the epidermis (acanthosis) due to an increase in keratinocyte turnover, which

contributes to adherent scales, raised and erythematous plaques which are densely infiltrated by T cells and dendritic cells (DC). Plaques are also very vascular with the growth of new vessels mediated by angiogenic factors such as vascular endothelial growth factor (VEGF).

PP is most often found on the outside of knees and elbows, the scalp, the lower back, the face, the palms of the hands and the soles of feet (See Figure 1).It is less common in areas such as the abdomen, nails, genitals, and intertriginous spaces. While psoriasis can affect various parts of the body's surface, with multiple forms (guttate, inverses, pustular, etc.), for simplicity this review will be focused primarily on PP.

Eruptions are due to multiple environmental and genetic factors. Several aspects of immune function dysregulation are critical parts of this manifestation. The roles of the innate and adaptive immune system have become apparent in recent years with regards to the pathogenesis of PP.

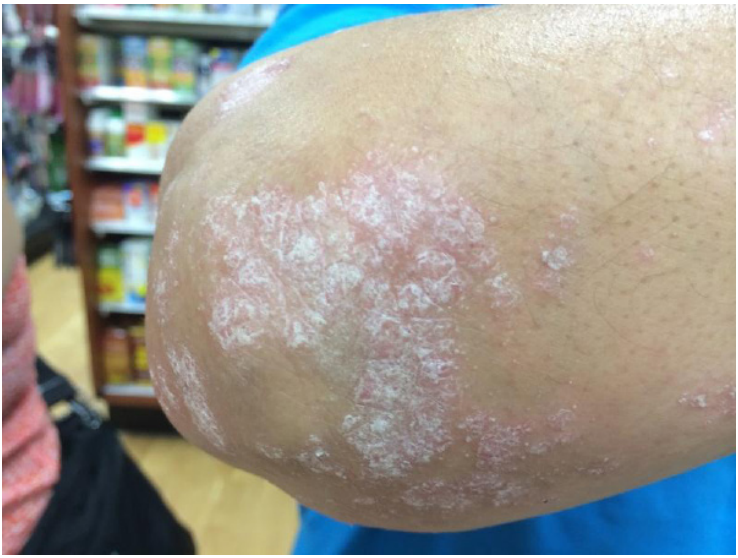

Figure 1: Digital image of a plaque psoriasis lesion located on the patient's right elbow.

Of the two main subsets of T lymphocytes, CD4 and CD8, the CD4 T lymphocytes are regarded as prolific cytokine producers. This subset can be further subdivided into Th1 and Th2, and the cytokines they produce are thus referred to as Th1-type and Th2-type. Th1-type cytokines [primarily Interferon gamma (IFNγ)] produce the proinflammatory response. In excess the proinflammatory response can lead to uncontrolled tissue damage. To balance this Th1-type mediated inflammation, Th2-type cytokines are produced which include interleukins (ILs) 4, 5, and 13 (involved in allergies) and also IL-10, which has more of an anti-inflammatory response.The development

of PP is mainly mediated by Th1, Th17, and IL-22-producing CD4+ T cells (where Th1 is T helper cells, type 1 and Th17 is T helper cells, type 17) [5]. It is also common for PP patients to have elevated levels of IL-6 especially in patients with psoriatic arthritis (PsA) which occurs in approximately 11% of patients with psoriasis [6]. IL-23 is produced mainly by activated antigen-presenting cells (APC) including dendritic cells (DC) which play a pivotal role in shaping the immune responses. IL-23 also regulates Th1 responses by stimulating IFNγ [7]. The production of chemokines attracts neutrophils whose role in the pathogenesis of PP remains unknown at this time [8]. (See Schematic 1)

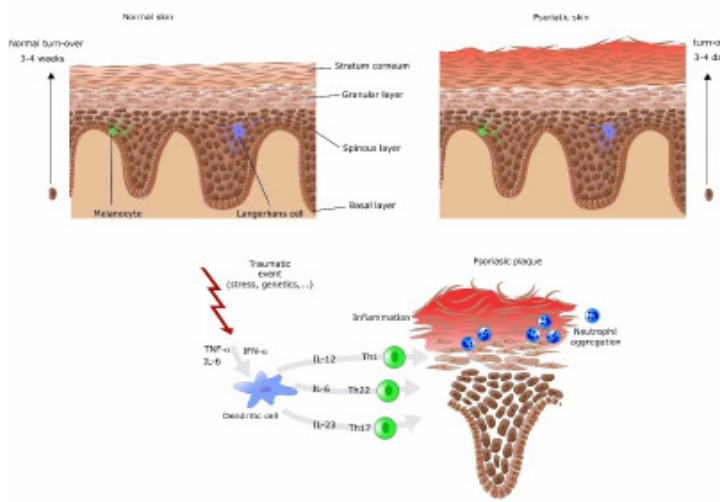

Figure 2: Schematic representation of the inflammatory pathway or psoriasis (*adapted from* ellepigrafica/Shutterstock.com).

The pathogenesis of PP involves dynamic interactions between multiple cell types and the numerous cytokines produced in response to triggers in those genetically predisposed. The list of triggers include stressful stimuli, such as infection (particularly streptococcal), oxidative stress, smoking, trauma (Koebner phenomenon) and/or drugs [9]. There are several drugs described in the literature that have been associated with the initiation, exacerbation, and aggravation of psoriasis (See Table 1). While certain drugs are more commonly associated as triggers (beta blockers, antimalarials and lithium) there is often no prediction of these occurrences and they became known only from case reports. These reports are also more common in patients with comorbidities and taking larger numbers of drugs [10].

Another probable trigger of PP is cadmium which can be toxic even at low levels. Common sources of exposure would be tobacco smoke and diet. Contaminated air and dust can be a source in areas near industrial sites or heavy road traffic. Cadmium can increase the risks of multiple-organ disease, metabolic syndrome, elevation of inflammatory markers and negative impact on the immune system. Higher blood levels of cadmium are associated with more severe PP [11].

Table 1: Examples of drugs or classes known to induce or aggravate psoriasis.

Drug or Class	Additional Information
Alcohol	Triggers and sustains eruptions
Amiodarone	Less commonly reported
Angiotensin-Converting Enzyme Inhibitors (ACE Inhibitors)	Usually seen in patients >50 years of age
Antibiotics	May be secondary to phototoxicity
Antimalarials	Most commonly associated
Benzodiazepines	Case-control study discovery
Beta blockers	Most commonly associated
Cimetidine	Less commonly reported
Clonidine	Less commonly reported
Digoxin	Less commonly reported
Fluoxetine	Less commonly reported
Gemfibrozil	Less commonly reported
Gold	Less commonly reported
Interferons	Observed in Hep C treatment
Imiquimod	Less commonly reported
Lithium	Most commonly associated
Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)	Case-control study discovery
Quinidine	Less commonly reported
Terbinafine	Fairly commonly reported
Tumor Necrosis Factor-alpha (TNF-α) inhibitors	Less commonly reported

Glycation is the non-enzymatic reaction between reducing sugars (glucose) and proteins, lipids or nucleic acids. The formation of advanced glycation end products (AGEs) is a complicated molecular process involving simple and at times, complex multistep reactions. AGEs are stress inducers of PP and can either be ingested from foods or be endogenously produced [12]. AGEs are highly oxidant, biologically active compounds that accumulate in tissues in association with hyperglycemia, hyperlipidemia and oxidative stress. Patients with severe psoriasis have accumulation of skin and serum AGEs, independent of associated metabolic disorders [13]. Since AGEs are highly oxidant, antioxidants are useful in helping to neutralize their activity. It is also possible to significantly reduced intake of dietary AGEs by increasing the consumption of fish, legumes, low-fat milk products, vegetables, fruits, and whole grains and by reducing intake of solid fats, fatty meats, full-fat dairy products, high glycemic and highly processed foods [14].

In response to stressful stimuli, keratinocytes may secrete a small molecular weight protein (an antimicrobial peptide) known as Cathelicidin LL-37 (LL-37) which is also involved in the pathogenesis of rosacea and atopic dermatitis.LL-37 interacts with DNA released by the dying cells to form complexes that activate Toll-like receptor 9 (TLR9) on plasmacytoid DCs in the dermis which produce interferon alpha (IFN-α) [15]. It is believed that

persistent over expression of LL-37 in psoriasis leads to uncontrolled IFN responses that drive autoimmune skin inflammation. IFN-α, along with other cytokines including TNFα, IL-6 and IL-1β,activates myeloid dendritic cells (mDCs) which induce the differentiation of Th1, Th17, and IL-22-producing CD4+ T cells in regional lymph nodes. These T cells move back into the dermis where they produce several inflammatory cytokines, including tumor necrosis factor (TNF-α), IFN-γ, IL-17, and IL-22(See Figure 3).These cytokines activate the keratinocytes stimulating proliferation and production of chemokines which are involved in the recruitment of more immune cells (neutrophils and mast cells) into the lesion. This recruitment action is important in sustaining disease activity [16].

Another important characteristic of PP is that the cytoskeletal protein keratin 17 (K17) is over-expressed in psoriatic epidermis which is induced by IFN-γ, and plays a role in the pathogenesis. IL-17A, and IL-22 are also known to upregulate K17 expression. K17 provides mechanical support to keratinocytes to maintain the integrity of the epidermis by heterodimerization with K6b (type II) into keratin heteropolymers and intermediate filaments network attached to desmosomes at points of cell–cell contacts [1]. K17 is a substantial antigen targeted by autoreactive T cells because of similar epitopes with streptococci and it promotes the proliferation and cytokines secretion of T cells.

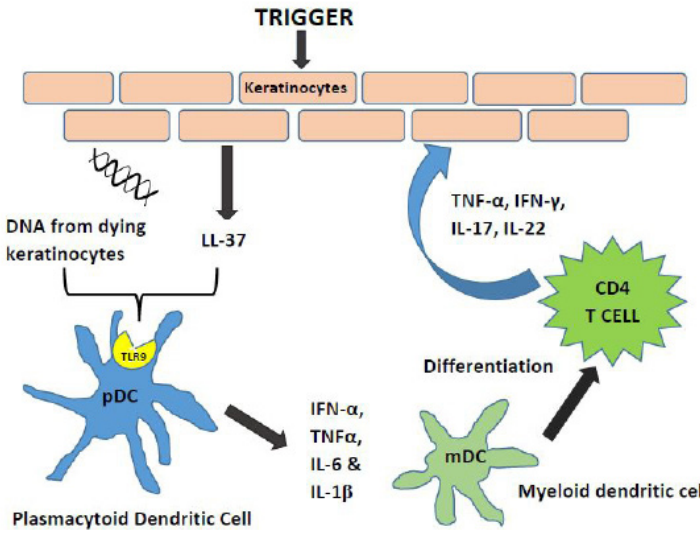

Figure 3: Schematic representation of LL-37 mediated inflammation.

Genetics

Genetic studies have identified over 20 different susceptibility genes associated with psoriasis, indicating the heterogeneous nature of the genetic susceptibility. Psoriasis genes fall into five main functional categories: those associated with acquired immunity (antigen presentation and helper T cell [TH] 17 activation), those associated with innate immunity (nuclear factor kappaB pathway signaling, type 1 interferon induction, and skin barrier

function). IL-17 can synergize with other cytokines, such as TNF and IL-22, for induction of key gene products related to the psoriasis phenotype [17].

It has also been shown that there are shared genes between psoriasis and diabetes. Researchers have implicated a T-cell receptor signaling pathway in the pathogenesis of psoriasis and further confirmed the shared genetic susceptibility between psoriasis and diabetes [18].

Comorbidities

Due to the extensive involved inflammatory process it comes as no surprise that PP is associated with major systemic comorbid conditions which complicate treatment. Of the 24 known comorbidities reported in one study from 469,097 psoriasis patients, the most common comorbidities were: hyperlipidemia, hypertension, depression, type 2 diabetes mellitus, and obesity. Those that affect ≥5% of patients also include: malignancies, serious infections, cerebrovascular disease, peripheral vascular disease, ischemic heart disease, osteoporosis, and cardiac dysrhythmia [19].

There is also an association of psoriasis and another autoimmune disease, multiple sclerosis (MS). Psoriasis may confer a disease severity-dependent risk of MS. Danish data shows the risk of the MS incidence rate for mild and severe psoriasis at 3.22 and 4.55 respectively compared to 1.78 for the reference population [20]. Data also points out that there is a significantly increased risk of myocardial infarction, stroke, and cardiovascular disease(CVD)

death in patients with psoriasis during stages of acute depression. Additionally, there is a bidirectional relationship between psoriasis and uveitis [21].

There is an association between psoriasis and the probability of patients having other autoimmune diseases. In one study patients with psoriasis were more likely to have at least 1 other autoimmune disease (odds ratio 1.6) and to have at least 2 other autoimmune diseases (odds ratio 1.9) with the strongest association being rheumatoid arthritis (odds ratio 3.6) [22]. In a retrospective study, evidence of association between psoriasis and Hashimoto's Thyroiditis (HT) was seen (odds ratio 2.49; 95% CI 1.79-3.48; $P < 0.0001$) [23].

The psychiatric comorbidities associated with PP are a major concern.In addition to the previously mentioned incidence of depression, other psychiatric manifestations include anxiety, severe depression, and suicidality, confirmed by multiple studies. The risk of suicide should be assessed in all PP patients but especially in adolescents and young adults, among whom the prevalence of skin disorders associated with suicidal behavior is higher. It is significant to note that female psoriatic patients report higher levels of depression than males [24].

The outward appearance of lesions has a negative impact on the body image which may lead to decreased self-esteem, potentially having a serious compromising effect

on the patient's quality of life. Some patients experience social isolation that can negatively impact their relationships, productivity, and careers resulting in cumulative impairment over a patient's lifetime. Many patients experience emotional effects such as anger and shame which should be recognized. Often a multidiscipline treatment approach is needed to include psychiatric consultation when these emotional and psychiatric issues exceed the realm of practice of dermatology [25].

One of the environmental factors suggested to play a role in the etiology and pathogenesis of psoriasis is diet. While studies have shown a strong association between psoriasis and celiac disease (CD) early evidence to suggested that a gluten-free diet may benefit some psoriasis patients [26]. Other patients with psoriasis have demonstrated an elevated sensitivity to gluten though not actual CD or allergy [27]. Gluten sensitivity with or without CD symptoms and intestinal pathology have been suggested as a potentially treatable cause of various diseases. As another T-cell mediated autoimmune disorder, D leads to inflammation, villous atrophy and crypt hyperplasia in the small intestine. Affecting a subset of individuals who experience sensitivity to wheat, in the absence of CD, there is systemic immune activation in conjunction with a compromised intestinal epithelium. These individuals are referred to as having non-coeliac wheat sensitivity (NCWS) and may experience a range of symptoms in response to ingestion of gluten, yet lack the characteristic

serological, histological or genetic markers of CD. NCWS patients show enhanced IgM responses to gliadin, lipopolysaccharides (LPS) and flagellin. A positive outcome for these patients however is the alleviation of symptoms on their withdrawal gluten from their diet [28].

There is an association with other autoimmune diseases and gluten intolerance. For example, increased prevalence of CD has been found in patients with autoimmune thyroid disease, type 1 diabetes mellitus, primary biliary cirrhosis, inflammatory bowel diseases and autoimmune adrenal failure. Considering the association of PP with potential gluten-induced intestinal inflammation, clinicians should question their psoriasis patients about symptoms of CD such as flatulence, fatigue, diarrhea, and history of iron-deficiency anemia. If symptoms are present then clinicians should test for anti-endomysial antibody (IgA EMA) or tissue transglutaminase antibodies (tTG-IgA), and with positive antibody results suggesting the potential benefit of a gluten-free diet [29].

If eliminating gluten from the diet reduces the recognized complications of CD and provides benefits in both general health and perhaps life expectancy, it may be inferred that patients with PP could benefit from such a diet change although research is lacking in this area. Some clinicians empirically have their patients eliminate gluten (and other inflammatory foods such as sugar and dairy products) from their diets for a period of 4 to 6 months to assess the outcome in the absence of testing. Testing

for gluten sensitivity is lacking at this time, however blind challenge with gluten could be considered the gold standard for making the determination.

Interestingly patients who eliminate these foods as a part of dietary changes for weight loss often report improvement in PP. Many of the other comorbidities of PP such as type 2 diabetes mellitus, hyperlipidemia and hypertension also show improvement from such elimination diets when weight loss is the expected result. Studies have shown that caloric restriction in obese subjects lowers the level of circulating inflammatory cytokines [30]. Individuals with sensitivity to wheat in the absence of celiac disease demonstratemeasurably increased serum levels of soluble CD14 and LPS-binding protein, and antibody reactivity to microbial antigens, indicating upregulation of systemic immune response. They also exhibit an elevated expression of fatty acid-binding protein 2 (FABP2) that correlates with the systemic immune responses to bacterial products, strongly indicating compromised intestinal epithelial barrier integrity and increased microbial translocation. They also show a significant change towards normalization in the levels of the immune activation markers, as well as FABP2 expression, in response to the gluten restrictive diet, which is associated with improvement in symptoms [28].

Obesity is associated with increased inflammation in part due to the production of adipokines and has a

central role in the development of metabolic syndrome. The prevalence of metabolic syndrome increased in the US from 32.9% in 2003-2004 to 34.7% in 2011-2012 [31]. According to TJ Love, etal., between 2003 and 2006 the prevalence of the metabolic syndrome was 40% among psoriasis cases and 23% among controls [32]. In psoriasis patients most of the prevalent comorbidities (hypertension, hyperlipidemia, type 2 diabetes mellitus, and obesity) contribute to metabolic syndrome that is associated with increased rate of heart disease and stroke [33]. Obesity is the most common comorbidity observed in children with psoriasis. In the 2003-2006 National Health and Nutrition Examination Survey, the prevalence of abdominal obesity was 62.9% in adult patients with psoriasis and 47.9% in patients without psoriasis. Clinicians should recognize and take this into account in the long-term treatment of PP [32]. Obesity has been linked with a decreased response to systemic and biologic therapies, in particular biological drugs in which dose is not weight-adjusted. In addition, obesity also increases the cost of treatment with drugs prescribed in weight-adjusted doses. Weight loss will decrease the risk of drug toxicity and enhance effectiveness and tolerance, particularly in the case of drugs administered at fixed doses [34].

Another aspect to consider concerning the comorbidities of PP is the higher healthcare resource utilization and the costs involved. Data shows that there are direct and indirect costs associated with short-term disabilities among patients with psoriasis in the United States (assumed to be

likely elsewhere too). Psoriasis patients with comorbidities used more healthcare resources than those without comorbidities. This data points out the need for adequate clinical and economic considerations in the choices of therapy for psoriasis patients with comorbidities [35].

Assessment

Treatment should be customized to suite the age of the patient, quality of life [QOL] issues, and patient needs. This is accomplished via adequate assessment looking at body location, characteristics of the psoriasis, body surface area (BSA), lesion thickness, severity of erythema, the extent of scaling, the social and emotional impact and the patient preferences.

The most common assessment tool of the severity of psoriasis in clinical trials is the Psoriasis Area and Severity Index (PASI) [36]. Other valid assessment tools include the Psoriasis Global Assessment (PGA) and the Lattice-System Physician's Global Assessment (LS-PGA) [37,38]. Another assessment tool is the Dermatology Life Quality Index (DLQI) which is a ten-question questionnaire used to measure the impact of skin disease on the quality of life [39]. This tool gives the clinician a way to measure impact from the patient's perspective which can prove valuable in the physician-patient relationship [40]. It is often valuable to use more than one measurement tool in research but not always necessary in clinical practice.

Treatment

The majority (about 80%) of patients affected with psoriasis have mild to moderate disease, and most of them can be efficaciously, safely and successfully treated with topical agents. Topical agents can also be used as adjunctive therapy for more severe cases. For example, those patients who are being concurrently treated with either ultraviolet light or systemic medications and usually not as monotherapy in those with recalcitrant disease. The expectation that no drug can cure this pathology seems to resonate as the advantages and disadvantages of each therapy reveal that there is no one perfect cure. We should therefore inform our patients that complete and total remission is not likely at the present time, however, attenuation of progression and a positive impact on severity can be achieved in most cases. Another key insight to treatment is that systemic treatments, either classical or biologics, may have a role in controlling the inflammatory burden, decreasing the likelihood of comorbidities, e.g. metabolic syndrome [41]. Choice of therapies should reflect the patient's preferences, disease severity, cost, compliance capabilities, comorbidities and effectiveness as treatment progresses. Therapy should treat the whole patient and not just their skin because their psychosocial wellbeing must be considered. It may also be wise, if appropriate, to touch the patient during the office visit to reinforce the notion that there is no fear of contagion and that they are worthy of empathy.

The treatment options presented here can be broadly categorized as topical pharmacologics, systemic pharmacologics (both biologic and non-biologic), non-pharmacologic (phototherapy), lifestyle (diet, stress), nutritional supplements and alternative therapies. Combinations of various treatments are often more efficacious, which are also mentioned herein. All of the treatment options covered in this chapter are those available in the US unless otherwise stated.

Topical Therapies

Commercially available topical therapies includes emollients and moisturizers, corticosteroids, keratolytics, anthralin, vitamin D3 analogs, calcineurin inhibitors, and retinoids. There are additional ingredients available through compounding (See Table 2). Compounding is the creation of a particular pharmaceutical product to fit the unique need of a patient by a pharmacist that has received proper training and who's laboratories is equipped with the quality ingredients & tools needed to formulate the prescription order. Often combinations of topical agents are more effective than when the drugs are used alone. The following section is a review of the commonly observed agents used in topical formulations, both manufactured and compounded. A brief review of these agents follows.

Anthralin (dithranol), a derivative of anthracene, has both anti-proliferative and anti-inflammatory effects via its strong reducing properties and inhibition of DNA syn-

thesis. Anthralin has limited evidence of efficacy in PP. It is not recommended for application to the face, genitalia, eyes, open sores, or mucous membranes because of painful irritation. It can also stain permanently fabric, skin, or hair, a yellowish-brown. Anthralin has been shown to be less effective than vitamin D derivatives and adverse events (AEs) limit its use to recalcitrant disease [42].

Vitamin D analogs – Calcitriol is the active form of vitamin D3 with more than twice the vitamin D activity of calcifediol.The mechanism of topical calcitriol in the treatment of plaque psoriasis is unknown but it has been hypothesized to modulate keratinocyte proliferation and differentiation [43]. Calcitriol is available in the US as a 3mcg/gm ointment for topical use to be applied twice daily and it is recommended not to exceed 200 gms per month. According to the American Academy of Dermatology (AAD), combining calcitriol with a topical corticosteroid is more effective than either treatment alone. In addition, fewer adverse events were reported with combination therapy in most clinical studies [44].

Calcipotriene [calcipotriol - (INN)] is a vitamin D analog that is structurally similar to naturally occurring calcitriol (the bioactive metabolite of cholecalciferol). Calcipotriene binds and activates vitamin D receptors resulting in inhibition of proliferation and induction of differentiation of keratinocytes in psoriatic tissue. It also binds to vitamin D receptors on lymphocytes suppressing proliferation.

Topically applying calcipotriene at a 0.005% showed improvements in approximately 50—70% of PP patients, although lesions can recur within 2—3 months following discontinuance. Research has also shown efficacy when calcipotriene 0.005% is combined with betamethasone dipropionate 0.064%, in both adults and adolescents [45,46].

Topical vitamin D derivatives have shown to be more effective than placebo.Vitamin D generally performed better than coal tar, but findings relative to dithranol were mixed [47].

Coal Tar is a distillate from coal that contains more than 10,000 compounds and likely works by DNA suppression. It is one of the oldest treatments known for psoriasis, and was used for many years before the advent of clinical trials. However randomized controlled trials show similar efficacy to calcipotriol. In one trial, 0.005% calcipotriol ointment produced a faster initial response and had better cosmetic acceptability, although at 12 weeks efficacy was similar to coal tar [48]. It is important to note that coal tar therapy is far less expensive than calcipotriol. The obvious disadvantage to coal tar use is that it has an unpleasant smell to some, it is messy and can stain. Coal tar has also been known to cause acne, photo-toxicity, irritation around the site of application and folliculitis in some patients [44].

In the medical practice, the use of topical corticosteroids is prevalent in psoriasis. Long term topical use of po-

tent steroids can possibly cause thinning of the skin, hypopigmentation and telangiectasia and thus should not be used with occlusive dressings. However, these AEs are rare in psoriatic plaque tissue even though topical steroid use is widely seen in therapy. In terms of efficacy, most corticosteroids perform better than placebo, with very potent steroids doing better than potent steroids [47].

Super potent topical steroids like clobetasol propionate are contraindicated in young children for fear of side effects like atrophy, depigmentation, and precipitation of pustular psoriasis on sudden withdrawal. Infants and children may beat higher risk for systemic effects secondary to enhanced absorption because of a larger skin surface area to body weight ratio and growth retardation is also a potential concern [49].

Cyanocobalamin has shown efficacy in the treatment of PP along with atopic dermatitis and eczema. It reduces nitrosative stress caused by nitric oxide free radicals [50-52]. Typical percentage of use is 0.07%compounded it in an emollient base and in studies was applied twice daily. It can be used in combination with other topical agents such as steroids, mast cell stabilizers and/or zinc pyrithione.

A cyclosporine topical liposomal formulation at 2.0% (w/w), was demonstrated to be effective in treatment of limited chronic plaque psoriasis with a satisfactory safety profile [53]. A compounded non-liposomal cyclosporine topical carbomer gel formulation is also available and referenced in the compounding literature [54]. Cyclosporine

can be used orally with the topical drugs calcipotriene and calcitriol. When used in conjunction with these topical formulations, lower doses of cyclosporine may be given, lessening the risk of side effects.

Ketotifen, a mast cell stabilizer and H1-antagonist antihistamine, is widely used in other countries outside the US as an oral agent for the management of bronchial asthma and other allergic disorders. However its long induction period and sedation limit the usefulness. It is FDA approved only for ophthalmic use in treating allergic conjunctivitis and therefore available as an API (Active Pharmaceutical Ingredient) for compounded medications. Ketotifen has been shown to decrease tumor necrosis factor secretion in human immunodeficiency virus (HIV) patients. Ketotifen for oral use has been investigated for use in other conditions such as atopic dermatitis, irritable bowel syndrome (IBS), neurodermatitis, chronic urticaria, and AIDS-associated wasting syndrome. Nasally it has been studied for allergic rhinitis. Structurally ketotifen is suitable be applied transdermally. In fact, ketotifen has been shown in animal studies to enhance transdermal patch delivery of other drugs [55]. These are the characteristics which have led to patent filings for topical use, however it is not commercially available in a topical/transdermal form at the present time as no products were yet launched. Topical ketotifen formulations are available via compounding.

Methotrexate has also shown efficacy when used topically for PP. A formulation of 0.1% in a suitable vehicle, applied twice daily for 6 weeks, demonstrated an overall improvement of 50% or more in the combined scores for erythema, scale, and elevation in the majority of the patients [56]. Please note the small percentage of use that should be applied only to affected areas. This decreased exposure makes it less likely to cause serious systemic effects. This formulation is only available as a compounded medication.

Naltrexone, a mu-opioid receptor antagonist, has been observed to help with itching in different dermatologic diseases (eczema, psoriasis and atopic dermatitis) [57,58]. In one small placebo-controlled pruritus study, more than 70% of the patients using the naltrexone 1% cream experienced a significant reduction of pruritus. This study showed a significant advantage of topically applied naltrexone over the placebo formulation and the findings were supported by the biopsy data from the open studies [59]. Topical naltrexone, as a single API or in combination formulations, is also available as a compounded medication.

Orally, low dose naltrexone [(LDN) doses usually between 1mg and 4.5mg nightly], used as an off-label therapeutic prescribed for a variety of immune-related disorders, has shown to cause an intermittent blockade of opioid receptors followed by upregulation of endogenous opioids. Patients diagnosed with MS have reduced serum levels of opioid growth factor (OGF) (i.e. [Met5]-

enkephalin) relative to non-MS neurologic patients, and LDN therapy restored their enkephalin levels [60]. Enkephalins are opioid peptides that can modulate immune responses and inflammatory processes. Furthermore, they inhibit keratinocyte proliferation and differentiation in vitro [61]. At present, LDN capsules are available through compounding pharmacies.

Pimecrolimus and tacrolimus are calcineurin inhibitors and have off-label recommendations for the treatment of severe, recalcitrant, plaque-type psoriasis. They are immunosuppressive by inhibiting the T-cell activation which affects the production of early cytokines, IL-2, IL-3, IL-4, granulocyte-macrophage colony stimulating factor (GM-CSF), and interferon gamma. The commercially available tacrolimus ointment or pimecrolimus cream require occlusion to penetrate the plaque sufficiently or to be compounded with salicylic acid to improve uptake. Both products have efficacy in the treatment of psoriasis and are considered safe and effective in patients with facial, intertriginous, and genital psoriasis.

These drugs do have a black box warning for a theoretical risk of cancer. Case reports of carcinoma have been published where tacrolimus was used in the treatment of lichen sclerosis [62]. They are not recommended in children under 2 years of age and they are a pregnancy category C but are generally not considered teratogenic due to their low systemic absorption [63]. An advantage often associated with topical calcineurin inhibitors (TCIs) is that

they do not cause thinning of the skin or hypopigmentation AEs like corticosteroids potentially do.

Salicylic Acid (SA), a beta-hydroxy acid, is used to remove excess keratin, by dissolution, in hyperkeratotic skin for many dermatologic disorders including PP and is thus referred to as a keratolytic. While used in higher percentages for other conditions, in PP the observed range of use is 2 to 6%, often in combination with other ingredients such as anthralin, coal tar and steroids.

Efficacy of salicylic acid alone in PP is not well documented due to its extensive use in combinations. There are many articles and studies published comparing the efficacy of different combinations involving salicylic acid [64]. In one review article of 19 studies, evidence was found to recommend the use of a combination regimen of topical corticosteroids and salicylic acid above monotherapy with either component [65].

A precaution when using SA is that it should not be used with other salicylate drugs. Also because of its physical presence on the skin it can block UVB and should not be applied prior to UVB phototherapy. Although transdermal absorption is minimal (≈10%), when applied in concentration over 20% of body surface area it can possibly be absorbed and affect hepatic and renal function. Chronic large surface area exposure may increase the risk for development of salicylism.

Tazarotene is a retinoid prodrug of tazarotenic acid which has regulatory effects on keratinocyte proliferation and differentiation. It was found to be effective and safe in the treatment of PP with acceptable tolerability [66]. One study compared its efficacy to fluocinonide (0.05%) and it was demonstrated that tazarotene is at least as effective as fluocinonide, and had a significantly better maintenance of therapeutic effect after discontinuation of therapy [67]. Tazarotene has been used in combination with salicylic acid and shown to have improved outcome versus tazarotene alone [68].

An older agent, urea (carbamide), improves water binding capacity and thus hydration of the stratum corneum and has mild keratolytic activity making it suitable for use in PP to reduce the hyperkeratotic state. It is also used to treat xerosis and for destruction and dissolution of dystrophic nails due to onychomycosis. In an older trial using a 10% ointment, patients showed a 2-fold increase in stratum corneum hydration, a small decrease in transepidermal water loss (TEWL) and a 29% reduction in epidermal thickness [69].

Table 2: Examples of topical agents for use in plaque psoriasis.

Drug	Mechanism of action	Observed percentages of use
Anthralin††	Inhibition of DNA synthesis	0.1 to 2%
Calcipotriene	Vitamin D derivative	0.005%
Calcitriol	Vitamin D derivative	3mcg/gm
Coal Tar††	Keratolytic	2 to 10%, higher strengths available
Corticosteroids††	anti-inflammatory, antipruritic, and vasoconstrictive	Varies by agent
Cyanocobalamin†	Neutralizes nitrosative free radicals	0.07%
Cyclosporine†	Calcineurin Inhibitor	1 to 2.0%
Emollients	Moisturizer	NA
Ketotifen†	Mast cell stabilizer, antihistamine	0.05%
Methotrexate†	anti-inflammatory, antiproliferative and immunosuppressive	0.1 to 1%
Naltrexone†	Anti-pruritic	1%
Pimecrolimus	Calcineurin Inhibitor	0.1%
Salicylic acid ††	Keratolytic	2 to 6%
Tacrolimus††	Calcineurin inhibitor	0.1%
Tazarotene	Inhibits epidermal hyperproliferation	0.05 to 0.1%
Urea††	Keratolytic	3 to 40%
Zinc Pyrithione††	Inhibits proliferations of keratinocytes	0.2 to 2%

† Available only through compounding
†† Available commercially and through compounding

Zinc pyrithione's action in PP is as a cytostatic agent but it also has anti-fungal and anti-bacterial activity useful for other indications. The cytostatic actions suppress cellular growth and multiplication, resulting in a reduction in the turnover of epidermal cells also making it suitable

for treatment of a hyperkeratotic state such as psoriasis. In psoriasis there is decreased spontaneous keratinocyte apoptosis in lesional skin [70]. A randomized double-blind clinical trial of topical zinc pyrithione with 60 patients showed the differences in the mean PASI scores before and after treatment were 2.4±2 and 0.4±0.1 in the treatment group versus the control group, respectively [71]. While not proving overwhelming results, the study clearly showed that zinc pyrithione can contribute to therapy, ideally in a topical combination.

For some perspective as to how well these topical treatments work, outcomes were evaluated in one meta-analysis review of RCTs for topical therapies (22,028 patients, 48 studies for trunk and limb psoriasis and 17 for scalp) with the majority of patients suffering moderate to severe disease. Patients receiving potent corticosteroids (alone or in combination with a vitamin D analogue), or very potent corticosteroids, dominated the treatment hierarchy at both sites (trunk and limbs, scalp). Other patients received coal tar and retinoids. All of the products used were licensed commercially available products and not compounded (or manufactured as referred to in the UK. Corticosteroids were found to be highly effective in psoriasis when used continuously for up to 8 weeks and intermittently for up to 52 weeks. Coal tar and retinoids were assessed to be of limited benefit and found to be no better than placebo [72].

A scalp psoriasis review article examined different treatment comparisons: steroid versus vitamin D, a compound combination of steroid and vitamin D versus steroid monotherapy and versus vitamin D. The results showed that steroids were more effective than vitamin D, the compound combination was better than steroid monotherapy and the compound combination was more effective than vitamin D [73].

Anthralin used in combined treatment with vitamin D/corticosteroid, and tazarotene all performed significantly better than placebo [47]. Topical corticosteroids compounded with salicylic acid may be valuable due to increased penetration by the salicylic acid of the corticosteroids thus improving efficacy [74]. Randomized trials have shown that corticosteroids compounded with vitamin D derivatives are more efficacious than either therapy alone and produce fewer side effects [75]. Use of topical tazarotene with a mid-, or high-potency corticosteroid increased efficacy while reducing the incidence of local adverse events [76].

About 60-90% of patients with psoriasis suffer from itching and the intensity of the itching is inversely related to QOL in patients with PP. The pathogenesis of itch in psoriasis is not fully understood though many theories involve neuropeptides. Effective treatment options are fairly limited and usually involve antihistamines, especially with a sedative effect, narrowband ultraviolet B, and antidepressants (doxepin, mirtazapine, paroxetine). Apremilast and biologic agents have also shown some efficacy in itch

intensity reduction. [77] If chronic pruritus is refractory or the cause is unknown, other agents to consider are capsaicin, calcineurin inhibitors for localized pruritus and naltrexone, pregabalin, ultraviolet therapy, and also cyclosporine for generalized itching. [78]

Compounded Medications

Topical combinations are available as "unlicensed manufactured specials" or "unlicensed extemporaneous preparations" in the UK or as referred to in the US as "Compounded Medications" from trained pharmacists. The active pharmaceutical ingredients (APIs) used in compounded medications are often older off-patent drugs. That fact along with the individualized nature of this method of treatment makes large-scale studies an impractical financial option so case studies are commonly used to disseminate information about the success and failure of compounded medications.

One such formulation was recently featured in a PP case report. The compounded formula containing Zinc Pyrithione 0.2%/Clobetasol Propionate 0.05%/Cyanocobalamin 0.07% Topical Cream was used to treat two large lesions of a 33-year old white male with a history of PP since the age of 19. After 3 weeks of therapy the patient's two treated lesions were reduced to flat, pink, smooth patches with complete resolution of plaque. (See illustration2.) [79].

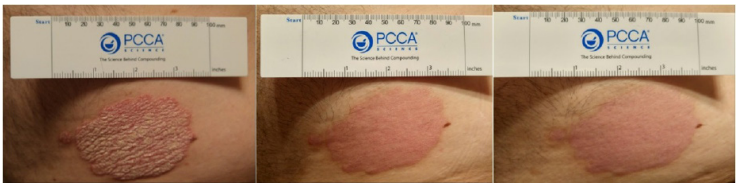

Figure 4: Digital images of the patient's left lower abdomen psoriasis lesion: before treatment, 1 week and 3 weeks after treatment (adapted from Jones et al., 2017).

The choice of the vehicle or base of the compounded medications can affect how well APIs penetrate the skin, thus influencing the efficacy of the treatment. These delivery systems include creams, ointments, solutions, gels, foams, sprays, shampoos, oils, and lotions. Many commercially available topical dermatologic products are not designed with sufficient emulsification systems to accommodate additional APIs. Some commercial products, with which dermatologist commonly request to have pharmacist compound multi-ingredient prescriptions, are only designed to hold just one API and often in a very small percentage. When additional ingredients are added to these products, it can overwhelm and break the emulsification system, becoming ineffective at delivery, and simply not pharmaceutically elegant.

Compounding bases or vehicles are designed to hold additional ingredients and can be developed with a disease state in mind. For example in treating psoriasis it is important that the base includes ingredients with emollient characteristics that may enhance the anti-inflammatory

properties of the APIs (avenanthramides, phosphatidyl glycerol, etc.). In a compounding base used to treat PP it is especially useful to have a combination that contributes to barrier function with ingredients such as a long chain ceramide to help restore the lipid bi-layer in the stratum corneum.

The importance of the compounding base was demonstrated using Enzyme-Linked Immunosorbent Assay (ELISA) for detecting IL-6 production in a psoriasis tissue model obtained from human skin tissue specimens with the following characteristics associated with psoriasis: increased cellular proliferation and cytokine release, and presence of psoriasis-associated biomarkers. Two commercial products (Mometasone Furoate Ointment USP 0.1% and Calcitriol 3 mcg/g ointment) were compared to two compounded versions prepared with the same concentrations of APIs in a compounding base designed to enhance the ingredients for psoriatic skin. The outcome showed that the compounded creams were superior in lowering IL-6 levels as compared to the commercial products [80].

JAK Inhibitors (Jakinibs) are a subset of the protein tyrosine kinases that block multiple aspects of cytokine signaling. Several Jakinibs have been studied for psoriasis but none have yet been approved. Oral tofacitinib is FDA approved for rheumatoid arthritis but did not get approval for psoriasis as an example, tofacitinib 2% ointment has been studied for topical use for PP and has shown to be ef-

ficacious. The ointment is not commercially available as a topical product and must be compounded at present [81]. While the preparation is not difficult to prepare, the cost of the API in the US is very expensive.

Ruxolitinib, another JAK inhibitor, is FDA approved for polycythemia vera and for intermediate and high risk myelofibrosis but it is not currently approved for use in psoriasis. It has been reported topically for alopecia universalis and in a small study for vitiligo with positive results [82,83]. When considering this drug for topical PP use, it is important to note that is it is also very expensive and usually not affordable if the patient is paying out-of-pocket. Third party coverage for compounded medications is variable at the present time usually requiring prior authorization.

Oral Therapies

Non-biologic systemic pharmacologics commonly used for PPinclude a retinoid, methotrexate, cyclosporine, sulfasalazine, tacrolimus, hydroxyurea, 6-thioguanine, azathioprine, fumaric acid esters and biologic agents. Systemic steroids are still prescribed though generally not recommended. (See Table 3.)

Acitretin, a synthetic retinoid, is approved for the treatment of adults with severe, recalcitrant psoriasis, including plaque, guttate, erythrodermic, palmar-plantar

and pustular types. It activates all three retinoic acid receptors (RARs) which modifies gene expression for epithelial cell growth and differentiation. It has demonstrated effectiveness in one trial of 46 adults 67.3% of patients reached 75% improvement in PASI scores (PASI75), and 89.1% of patients had at least 50% improvement (PASI50). A total of 39% of patients experienced at least one AE but none severe enough to discontinue treatment [84]. Arthralgia and spinal hyperostosis (progression of existing lesions) were reported at an incidence of 10—25% in clinical trials.

Apremilast inhibits phosphodiesterase 4 (PDE4) which degrades intracellular cAMP in both immune cells and keratinocytes. A subsequent increase in cAMP can lead to a decrease in the production of proinflammatory cytokines TNF-a, IL-2, IL-12, IL-23, and interferon-γ; and also an increase anti-inflammatory cytokines (IL-10) and also to reduce epidermal thickness. In a multicenter, randomized, placebo-controlled study, apremilast was shown to be effective in the treatment of moderate-to-severe plaque psoriasis over 52 weeks [85]. There are no sustained significant laboratory abnormalities associated with apremilast treatment so lab monitoring is generally not necessary and the AEs profile is not significant in most patients. No opportunistic infections have been seen [86]. Apremilast may be sufficient as a monotherapy in up to one-third of patients with moderate to severe PP. Case reports show that Apremilast has been used successfully in combination with adalimumab and secukinumab for pa-

tients that failed on other therapies [87,88]. A chart review study showed that apremilast can be safely and effectively combined with phototherapy, systemic, and/or biological agents in patients with plaque psoriasis not responding adequately to these agents alone. Gastrointestinal side effects were manageable in the majority of patients [89].

Cyclosporine was originally used for acute myeloblastic leukemia but is now FDA approved for multiple indications including the treatment of severe, plaque-type psoriasis in immunocompetent patients who failed to respond to at least one systemic therapy (e.g., PUVA, retinoids, methotrexate) or in patients for whom other systemic therapies are contraindicated or cannot be tolerated. Cyclosporine induces immunosuppression by inhibiting the first phase of T-cell activation which causes transcriptional activation of immediate and early gene products (e.g., IL-2, IL-3, and IL-4, TNFα, and IFNγ) thus slowing T-cells progress. While its mechanism is complex it ultimately is a calcineurin inhibitor. The adverse events (AEs) profile of cyclosporine is extensive and includes many severe AE's including: angioedema, heart failure, myocardial infarction and bone fractures [90]. It commonly causes hypertension, headache, hypertrichosis, gingival hyperplasia, nausea, and increased susceptibility to infections. Despite its high rate of AEs, it has been used in pregnancy (Category C) with the short-term use or lower doses when risk versus benefit is established [91].

The stance that oral steroid use in PP is generally not considered a good therapeutic choice seems to be the dominant published opinion. The well-known problems with systemic use is that they can cause immunosuppression, adrenal suppression of endogenous production of cortisol (and/or manifestations of Cushing's syndrome in some patients) and abrupt withdrawal can cause flares in psoriasis. However, there are opinions on both sides of the argument and prescribing habits still show, as of a few years ago, that oral steroids are used to some extent [92].

Dr. Mark Lebwohl [93] is quoted on the National Psoriasis Board website as saying "If patients with psoriasis are prescribed oral steroids, that's a mistake", "Withdrawal of systemic steroids is the most common precipitating factor in developing pustular or erythrodermic psoriasis, rare life-threatening forms of the disease." [https://www.psoriasis.org/advance/what-you-need-to-know-about-steroids]

Hydroxyurea is an antimetabolite that is thought to cause inhibition of DNA replication. Data suggest that hydroxyurea is inferior to methotrexate in short-term use (3 months) versus long-term use (9-16 months) where it may be more effective. Hydroxyurea possibly represents an alternative to methotrexate in patients who experience intolerable side effects (e.g. bone marrow suppression) or who have reached the recommended cumulative dose of methotrexate [94,95].

Table 3: Examples of non-biologic oral agents for plaque psoriasis.

Drug	Mechanism of action
Acitretin	Retinoid - normalize the keratinocyte growth cycle
Apremilast	Phosphodiesterase 4 inhibitor
Azathioprine	Immunosuppressive, may inhibit DNA and RNA synthesis
Corticosteroids	Anti-inflammatory, antipruritic, and vasoconstrictive
Cyclosporine	Immunosuppressive, calcineurin inhibitor
Fumaric acid esters	Suppress Peripheral CD4- and CD8-Positive Lymphocytes
Hydroxyurea	DNA replication inhibition
Methotrexate	Anti-inflammatory, antiproliferative and immunosuppressive
Mycophenolate mofetil	Immunosuppressive by inhibiting lymphocyte purine synthesis
Tacrolimus	Calcineurin inhibitor
6-thioguanine	Blocks synthesis and utilization of purine nucleotides
Leflunomide	Dihydroorotate dehydrogenase and tyrosine kinase activity inhibitor

Leflunomide is not widely used for treating PP primarily due to AEsand lack of efficacy. Leflunomide is a disease-modifying antirheumatic drug (DMARD) approved for the treatment of rheumatoid arthritis (RA) and has other off-label uses. It has been studied in patients with both PsA and psoriasis. One randomized controlled trial published in 2004, reported the mean relative reduction in PASI score was 24.1% for leflunomide compared with a reduction of 6.3% for the placebo group but higher reported rates of diarrhea in the treatment group [96,97].

Methotrexate (MTX) is approved for the symptomatic control of severe, recalcitrant, disabling psoriasis that is not adequately responsive to other forms of therapy and only when the diagnosis has been established, as by biopsy and/or after dermatologic consultation [98]. MTX, the oldest systemic therapeutic agent for PP, increases the

endogenous levels of adenosine which is a potent anti-inflammatory substance. In a randomized, double-blind, placebo-controlled 16 week study, 35.5% of subjects achieved a 75% reduction in PASI and the authors concluded that it was a reasonable expectation of oral methotrexate efficacy to be that approximately 40% of patients will achieve PASI 75 [99]. MTX inhibits dihydrofolate reductase, resulting in a decreased supply of folates. The most common of these AEs are nausea, diarrhea, fatigue, and headache which may be mitigated by folinic acid supplementation because AEs of low-dose MTX in patients are related to folate antagonism and/or folate deficiency. The use of folic acid (FA) in patients being treated with MTX for PP seems to lead to less discontinuation and does not appear to have a significant effect on efficacy. Based on evidence from RCTs the use of FA is recommended for patients receiving MTX for PP, though the dosing and frequency is debatable, varying from 1 to 5 mg/day (except on the day of MTX administration) to 5 or 10 mg/week, 24 or 48 h after MTX. It is important to note that typical dosages of MTX for PP (10 to 25 mg given orally as a single weekly dose or alternatively 2.5 PO every 12 hours for 3 doses every week) are much lower than those for the treatment of neoplastic disease (up to 900—30,000 mg/m2 IV with leucovorin rescue) [100].

MTX monitoring parameters include: CBC with differential, chest x-ray, LFTs, PFTs, pregnancy testing, serum albumin, serum creatinine/BUN, serum electrolytes

and serum uric acid. Cirrhosis, aplastic anemia, bone fractures, bradycardia, coma, hepatic failure, pancreatitis, pulmonary embolism and ventricular tachycardia are among the most severe AEs.

Mycophenolate mofetil (MMF) is metabolized to mycophenolic acid, an inhibitor of de novo purine synthesis in B and T cells and was used in transplant medicine before being used off-label in dermatology. Two open-label studies have shown significant efficacy in improvement of PASI scores [101,102]. Side effects (commonly nausea and diarrhea) often limit therapy. Serious AEs include hematologic malignancies, progressive multifocal leukoencephalopathy, and other serious infections. MMF can also cause reversible hematologic abnormalities which mandate complete blood count monitoring along with electrolytes and LFTs. MMF is a pregnancy category D and female patients should be screened before initiating therapy. A pregnancy category D means that there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks. In general, MMF is a reasonable alternative therapy for patients who have failed both oral and biologic medications.

Thioguanine [6-thioguanine (6-TG)] is an antimetabolite that is the active form of azathioprine and is an off-label recommendation for PP. Azathioprine is approved for the treatment of psoriasis but should generally

be reserved for psoriatic patients who have failed multiple other therapies due to the potential for severe adverse effects. The 6-TG is approved for use in acute myelogenous leukemia (AML). As an older agent that became popular in the treatment of PP about the same time as methotrexate its prescribing frequency has declined because of the possibility of severe bone marrow depression. Myelosuppressive effects of thioguanine can increase the risk of infection or bleeding, so precautions should be taken prior to dental procedures and surgery. Thioguanine is a pregnancy risk category D drug and it is not known whether it is distributed into breast milk. Pediatric dosage regimens exist and are FDA approved for AML only.

In terms of thioguanine efficacy in PP, two older studies demonstrated 78% complete or almost-complete clearance and effective maintenance in 49%of patientson varying doses [103,104]. It was observed that with pulse-dosing therapy the incidence of bone marrow suppression appears to be greatly reduced [105].

Sulfasalazine has been prescribed off label orally to treat PP, though it is not widely used. In one study marked improvement was observed in 41% of patients; moderate improvement was observed 41% of patients as well, however side effects were prevalent (rash and nausea) with a 23% dropout rate at 8 weeks [106].

Dimethyl fumarate, a Fumaric acid ester (FAE), is approved for use in MS, another T cell-mediated autoimmune disease. FAEs are licensed for the treatment of pso-

riasis in Germany. In a review, the evidence was limited and the conclusions suggest that FAEs are superior to placebo and possibly similar in efficacy to MTX for psoriasis. Short-term studies reported no serious adverse events, however nuisance adverse effects, including flushing and gastrointestinal disturbance, were observed [107].

Biologics

Systemic pharmacologic treatments include biologics which are protein-based drugs derived from living cells cultured in a laboratory. Biologics are different from general immunosuppressive drugs in that they target specific parts of the immune system. As of this date there are nine commonly prescribed biologics for the treatment of PP available in the US which are administered via subcutaneous (SQ) injection or intravenous infusion and are usually only given to patients with moderate to severe disease. The general mechanisms of action of these substances involve TNF-alpha inhibition, IL-17 inhibition or IL-12/23 inhibition. (See Table 4.)

Biologics are indicated for the treatment of moderate-to-severe plaque psoriasis and are generally considered as second/third-line use after topical treatments, phototherapy (for suitable patients), UVA-PUVA (psoralen plus UVA), and systemic medications (immunosuppressants). Biologics are generally used to treat adults who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapies including cyclosporine, methotrexate (MTX) or PUVA. While previously ap-

proved for pediatric use in Europe, in 2016 the FDA approved etanercept for treatment of chronic moderate to severe plaque psoriasis in children ages 4 to 17.

Table 4: Examples of biologics for plaque psoriasis.

Drug	Mechanism	Administration
Adalimumab	TNF-alpha inhibitor	SQ Injection
Brodalumab	IL-17 inhibitor	SQ Injection
Certolizumab Pegol†	TNF-alpha inhibitor	SQ Injection
Etanercept	TNF-alpha inhibitor	SQ Injection
Guselkumab	IL-23 inhibitor	SQ Injection
Infliximab	TNF-alpha inhibitor	IV Infusion
Ixekizumab	IL-17 inhibitor	SQ Injection
Secukinumab	IL-17 inhibitor	SQ Injection
Ustekinumab	IL-12/23 inhibitor	SQ Injection

†Off-label recommended

Biologics are indicated for the treatment of moderate-to-severe plaque psoriasis and are generally considered as second/third-line use after topical treatments, phototherapy (for suitable patients), UVA-PUVA (psoralen plus UVA), and systemic medications (immunosuppressants). Biologics are generally used to treat adults who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapies including cyclosporine, methotrexate (MTX) or PUVA. While previously approved for pediatric use in Europe, in 2016 the FDA approved etanercept for treatment of chronic moderate to severe plaque psoriasis in children ages 4 to 17.

The major safety concerns for biologics are extremely important to consider and include increased risk of serious infections and malignancies. Manufacturers have placed

black box warnings in their product literature that warn of increased risk for developing serious infections that may lead to hospitalization or death. These infections include tuberculosis, including reactivation of latent tuberculosis; invasive fungal infections, including histoplasmosis, coccidioidomycosis, candidiasis, aspergillosis, blastomycosis, and pneumocystosis; and lastly bacterial, viral, and other infections due to opportunistic pathogens, including Legionella and Listeria. Clinicians should closely monitor patients for signs and symptoms of infection throughout their course of therapy and for a reasonable time period following discontinuation.

The warnings of malignancy include lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers. The incidence rates of infections and malignancies vary between indications of use with biologics. Further research is needed regarding the safety of individual anti-TNF biologics and to clarify their impact on the different immune-mediated inflammatory diseases [108].

Another concern for their use is the risk of inducing antidrug antibodies (ADA). This may lead to provocation of an immune response that may result in serious clinical consequences, such as the decreased efficacy of the drug and infusion or injection site reactions. Chimeric antibodies that are similar to human antibodies, but carry a larger stretch of non-human protein, have been shown to

be more immunogenic than humanized or human antibodies. In studies monitoring infliximab in rheumatoid arthritis and inflammatory bowel disease there are reports of increased anti-infliximab antibodies,[109]there was however no confirmation of this phenomenon in dermatologic patients. In a review antibodies against infliximab were reported in 4 studies ranging from 4 to 43.6% of patients, a very wide range of variance [110].

In a more recent study the incidence of anti-infliximab antibodies was low, and a correlation was observed between the presence of antibodies, an absence of infliximab concentration, loss of clinical response and the development of infusion reactions. Clinical response was good and toxicity low when infliximab concentrations were higher than 0.05 μg/ml [111]. Low concentration of drug appears to be a relative factor in the development of ADA. In a recent systematic review biologic/biosimilar immunogenicity differs among agents used to treat several inflammatory diseases including psoriasis, with the highest rates observed with infliximab and adalimumab [112]. The formation of ADA with biologics may prevent patients from achieving a full clinical response [113].

In addition to the black box warnings, typical precautions and contraindications of TNF-alpha inhibitors include warnings for use in children and neonates, pregnant patients or pregnant partners of patients, nursing mothers, patients with bone marrow suppression, the elderly, pa-

tients with hepatitis B or C virus infections, HIV patients, MS patients, patients on corticosteroid therapy, diabetes mellitus patients, patients with malignant neoplasms, irritable bowel disease, ulcerative colitis, and those undergoing elective surgery. Administration of live vaccines must be avoided in patients being treated with biologics under all circumstances.

Adalimumab is a monoclonal antibody that binds to TNF-alpha and has 100% human peptide sequences. It is administered by SQ injection and is FDA approved for the treatment of moderate to severe chronic PP in patients who are candidates for systemic therapy or phototherapy, and when other systemic therapies are medically less appropriate. It has shown efficacy at 16 weeks where 71% of patients achieved greater than or equal to 75% improvement in the PASI score [114].

Brodalumab, an injectable human IgG2 monoclonal antibody that binds to IL-17 receptor A, was FDA approved early in 2017 for the treatment of moderate to severe plaque psoriasis in patients who are candidates for systemic therapy or phototherapy and have failed to respond or have lost response to other systemic therapies. Because of its association with suicidal ideation and behavior it is only available via a restricted program for which prescribers must be certified in order to prescribe. The incidence of serious infections in trials was 0.5% for brodalumab and 0.2% for placebo. Moderate AEs include

antibody formation, bleeding, erythema, meningitis and neutropenia. Injections site reactions were generally mild [115]. In phase 3 studies, treatment with brodalumab resulted in a rapid (4 weeks) reduction in the signs and symptoms of psoriasis, twice as fast as with ustekinumab [116].

Certolizumab pegol is attached to polyethylene glycol (Pegylated) and is a unique anti-TNF biologic that contains a Fab (fragment antigen binding) fragment of a humanized antibody that is a potent neutralizer of TNF-alpha. It is FDA approved for the treatment of Crohn's disease, ankylosing spondylitis, psoriatic arthritis and rheumatoid arthritis, but has an off-label recommendation for psoriasis. Unlike adalimumab, infliximab, and etanercept, certolizumab pegol does not have a fragment crystallizable region and thus, does not fix complement or cause antibody-dependent cell-mediated cytotoxicity [117].

Etanercept binds to and inactivates TNF but does not affect TNF production or serum levels. It may also modulate adhesion molecules, other serum cytokines and serum matrix metalloproteinase-3. It is usually administered subcutaneously twice weekly and is FDA approved for the treatment of chronic moderate to severe plaque psoriasis patients who are candidates for systemic therapy or phototherapy [118]. Efficacy was established in one 24-week, double-blind study using 50mg twice weekly, yielding a 75% improvement in the PASI 75 for 59% of patients [119].

Guselkumab is FDA approved for the treatment of moderate to severe plaque psoriasis in those patients who are candidates for phototherapy or systemic therapy and is the most recent biologic to be released (2017) as of this writing. Guselkumab also reduces serum concentrations of IL-17A, IL-17F, and IL-22 relative to pretreatment concentrations in patients. AEs include diarrhea and gastroenteritis developed in less than 2% of patients tested. Additional AEs included headache (<5%), arthralgia, and migraine. Injection site reactions (erythema, bruising, hematoma, bleeding, swelling, edema, induration, inflammation, pain, skin discoloration, pruritus, and urticaria) developed in 4.5% of patients in the trials [120].

There are two studies concerning guselkumab efficacy published from the phase III trial [121,122] The Reich K, et al. study looked at randomized withdrawal and retreatment with results showing guselkumab is a highly effective, well-tolerated, maintenance therapy, including in adalimumab non-responders. The Blauvelt A, et al. study looked at continuous treatment showing that guselkumab demonstrated superior efficacy compared with adalimumab and was well tolerated in patients with psoriasis through 1 year.

Infliximab neutralizes the biological activity of TNF-alpha and prevents high affinity soluble and transmembrane forms from binding with its receptors. Infliximab

reduces infiltration of inflammatory cells within the plaques and may reduce epidermal thickness [123]. With regards to infliximab's efficacy, clinical trials showed that 80% of patients achieved at least a 75% improvement in the PASI 75 at week 10 and nearly half of the treated patients achieved PASI 90 [124].

Ixekizumab was approved for use in PP in the spring of 2016 and is approved for moderate to severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy. It is monoclonal antibody that selectively binds to the IL-17A cytokine, inhibiting its interaction with the IL-17A receptor [125]. Ixekizumab is administered by SQ injection on a specified schedule. Data from three trials were integrated showing that improvements were noted at one week and continued through week 12. Mean regional PASI improvements at week 12 were ≥84.2%, with improvements for head/neck at 91.4% and trunk area at 92.8% [126].

Secukinumab is a human IgG1 monoclonal antibody that selectively binds to the IL-17A cytokine itself, preventing it from engaging its receptor, thus decreasing the normal immune inflammatory response and potentially reducing epidermal neutrophils in psoriatic plaque. It is administered via SQ injections and was approved in January 2015 for moderate to severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy

[127]. One phase III trial reported the proportion of patients who met the criterion for PASI 75 at week 12 was higher with each secukinumab dose than with placebo or etanercept. The percentage of patients that met the criterion at the 300mg dose was 81.6%.

Ustekinumab is an IL-12 and IL-23 antagonist, a human IgG monoclonal antibody that binds to a protein subunit of both IL which are elevated in PP. The binding disrupts IL-12 and IL-23 signal transduction reducing immune and inflammatory mechanisms. IL-12 usually stimulates CD4+ T cells to develop into Th1cells which produce interferon gamma and mediate cellular immunity and IL-23 usually stimulates CD4+ T cells to develop into IL-17 producing T cells (Th17). In summation ustekinumab decreases IL-12 and IL-23-induced interferon-gamma, IL-17A, TNF-alpha, IL-2, and IL-10 secretion [128]. In clinical trials ustekinumab was deemed to be efficacious for the treatment of moderate-to-severe psoriasis and, following initial therapy with maintenance dosing every 12 weeks, maintains efficacy for at least a year in the majority of patients. The majority of patients achieved PASI 75 at week 12 of the study [129].

In terms of efficacy in a short-term head-to-head trial, ustekinumab was shown to be moderately more efficacious and had a lower incidence of injection site reaction than etanercept. Indirect comparisons suggest that infliximab may be the most efficacious; however, there is

no definite evidence to support that there is a difference among adalimumab, etanercept, and infliximab in terms of efficacy. Weak evidence suggests that adalimumab may be associated with higher risk of paradoxical psoriasis, and that adalimumab and infliximab may be associated with a higher rate of tuberculosis than etanercept [130]. Head to head comparison of ixekizumab versus etanercept showed that mean regional PSAI at week 12 was ≥84.2% for ixekizumab versus ≤70.9% for etanercept in all regions [122].

In contrast to the positive clinical data supporting the successful treatment of PP, and not considering the potential health risk of these therapies, biologic drugs are expensive. In 2011 a study showed estimated annual cost for the treatment of psoriasis in the US to be approximately 11.3 billion dollars with an expanding biologics segment. At that time annual treatment with MTX was approximately $1,330 contrasting with $48,731 for high-dose etanercept [131]. In 2014 another study published the cost of one year of induction and maintenance treatment was highest for ustekinumab ($53,909), followed by etanercept ($46,395), and adalimumab ($39,041). The sales-based cost of drugs was greatest for ustekinumab ($25,012), then adalimumab ($6,786) and etanercept ($6,629). Sales-based cost increased at an average of 20% per year [132].

Annual cost of biologics at label use recommendations are already high but many patients often require above-label dosages. A retrospective analysis was done

using a large US claims database for 3,310 patients treated between January 2010 and June 2012.Patients were over 18 years old, diagnosed with psoriasis and were using either etanercept, adalimumab or ustekinumab. It was observed that many patients were taking above-label doses (>10% of indicated in the product label) for ≥ 180 days over a 12 month period following the maintenance period. Extensive above-label use occurred in 20% of etanercept patients, 2.6% of adalimumab patients and 14.8% of ustekinumab patients. Additional annual cost (beyond indicated label dosage recommendations cost) per patient was $19,458 for etanercept, $18,972 for adalimumab and $21,045 for ustekinumab. This accounts for over $7.6 million in higher annual cost [133].

Non-Approved Biologics

Several products have been investigated for use in PP but are not yet approved or some products have been rejected for approval by the FDA. Certolizumab Pegol, a TNF-alpha inhibitor administered by SQ injection, is currently in phase 3 clinical trial for psoriasis and has shown an 83% PASI 75 response rate with no unexpected safety issues. It has not received FDA approval for PP but has off-label use [134].

Amongst those being looked at for possible PP use is abatacept, which is a fully human recombinant fusion protein that is a T-cell inhibitor administered by IV infusion,

approved for use in rheumatoid arthritis is being studied for use following ustekinumab in the treatment of PP.

Another biologic being looked at is golimumab. Data is lacking for the use of golimumab, a TNF-alpha inhibitor (approved for use in ankylosing spondylitis, psoriatic arthritis, rheumatoid arthritis and ulcerative colitis), in the treatment of PP although there is a successful case report of its use in erythrodermic psoriasis [135].

Though not yet approved, the manufacturers of tildrakizumab, an investigational IL-23p19 inhibitor, filed a Biologics License Application with the FDA in May 2017. It is expected to be approved as the phase III trials are touting efficacy compared with placebo and etanercept [136].

An additional drug on the horizon for psoriasis ispiclidenoson, a first-in-class oral A3 adenosine receptor antagonist (A3AR). Mechanisms include: apoptosis inhibitor, immunosuppressants, IL-17 receptor antagonists; IL-23 receptor antagonists; currently in clinical trials for autoimmune diseases including psoriasis.

The FDA turned down the approval of tofacitinib (10mg tablets) for the treatment of psoriasis in 2015 but the oral drug is currently approved for the treatment of rheumatoid arthritis. The rejection was not due to lack of efficacy but centered around safety issues of hyperlipidemia, increased incidences of serious infections (specifically the reactivation of herpes zoster), and nonmelanoma skin cancer.

Non-Pharmacologic

Phototherapy

The common types of light therapy used in the management of PP include broad and narrow band UVB, PUVA, combined therapy including home phototherapy and the Excimer laser. UVB treatments can be done in office, clinic, or at home with a phototherapy unit. Laser treatments are restricted to the office only and UVA is only effective with sensitizing with a chemical agent such as psoralen. Consistency is key to all successful phototherapy options.

Early research described an up-regulation of Th2 cytokines (enhanced transcription and expression of IL-10) in response to UVB phototherapy. There is also evidence of down-regulation of the Th1/Th17 pro-inflammatory pathways in PP from UVB therapy. Decreases in IL-12, IL-17, IL-20, IL22, and IL-23 have been observed [137]. Induction of apoptosis is another mechanism of UVB therapy for PP. In one study it was found that UVB therapy led to selective apoptosis and profound depletion of T lymphocytes in epidermal psoriatic tissue, but minimally in the dermis. It thus appears that there are several mechanisms working on concert with UVB therapy. UVB therapy alone may not be entirely effective in all patients, certainly not those with severe presentation [138].

Methoxsalen (psoralen) is activated by long wavelength UV radiation and is a potent erythemogenic,

melanogenic, and cytotoxic therapy. Most patients experience erythema starting several hours after therapy and lasting for 48 to 72 hours. This inflammation is followed over several weeks by repair that is characterized by increased melanization of the epidermis and thickening of the stratum corneum. Methoxsalen, in addition to being a sensitizing agent for UVA, is also a photosensitizer so general precautions should be observed [139]. PUVA therapy, which requires compliance for 9 to 15 weeks for maximum outcome, may be a viable option for patients who have failed UVB therapy. This therapy can provide long-lasting remission in some cases and efficacy in 80% of patients (PASI-75), which is comparable to some of the biologics available [140].

Heliotherapy (sunlight) can also be employed for some patients if applicable for their geographic location and season. Tanning beds are usually UVA only and are not supported for phototherapy for PP.

Goeckerman therapy (GT) includes use of 2-4% crude coal tar topical compound for 2 hours or longer and then exposed to broad-band ultraviolet B (UVB) radiation, narrow band UVB may also be used. It has been shown that this type of therapy reduces epidermal DNA synthesis. In a trial using a modified version of GT 95% reached PASI 75 and most of the patients were discharged within 2 months [141]. GT can still be an important part of PP therapy. GT's safety profile is excellent in comparison to oral systemic therapies like cyclosporine, methotrexate or

biologics. It also does not carry the same risks as biologics for serious complications like cancer, infections, and increased cardiovascular problems [142].

Excimer laser therapy showed efficacious treatment with a favorable remission retain a 9-month pilot study. Of the 12 patients that completed the study, 54% achieved PASI 75 [143]. In a second study utilizing twice weekly treatments with a 308-nm excimer laser combined with clobetasol propionate twice daily for a month followed by calcitriol ointment twice daily for the next month, 83% of 30 patients achieved PASI75 at 12 weeks [144].

Lifestyle, Nutritional Supplements and Alternative Therapies

Lifestyle

Lifestyle

As with gluten sensitivity (see section 5. Comorbidities), other proflammatory foods in a patient's diet can play a role in the onset and maintenance of PP. GI inflammation can give way to permeability problems in gut health and in Th1/ Th2 balance. In a recent survey the most common psoriasis triggers reported by respondents were sugar, alcohol, nightshades, and gluten with prior studies implicating that these dietary components cause alterations in the intestinal microbiome composition, irritation of the intestinal lining, and upregulation of the immune system. There is evidence suggesting that simple sugars in the diet

lead to dysbiosis of the gut microbiome favoring injurious bacterial taxa and an increase in inflammatory cytokines. Evidence also suggests that complex carbohydrates with high fiber, such as those found in fruits and vegetables, have been found to have an opposite effect on the gut microbiome and reduce inflammation [145].

Stress

In a modern world there is stress from physical, mental, or emotional sources causing bodily or mental tension. Prolonged stress triggers a series of changes in the brain and body. Initially stress activates the hypothalamus-pituitary-adrenal (HPA) axis and sympathetic nervous system (SNS) which upregulates the levels of glucocorticoid (GCs) and catecholamines (CAs), and they in turn inhibit the secretion of proinflammatory cytokines directly or indirectly while promoting the secretion of anti-inflammatory cytokines.

Stress causes inflammation which can trigger PP and PP causes psychological stress for the patient. Dr. John Koo [146] said that inflammation is the body's way to cope with stress, and he suspects the immune system responds the same way to mental stress [147]. Managing stress impact thus becomes a meaningful part of disease management as well.There is a correlation between psychological stress and the clinical severity of symptoms.The more stress mentally affects the patient, the more severe the dermatologic lesions. Also stressful events constitute a major risk for the occurrence, recurrence and/or the exacerbation of the severity and duration of the symptoms [25].

Stress management was recently studied in graduate students and many methods demonstrated a reduction in perceived stress post intervention. Interventions varied from a stress management course to mind-body-stress-reduction (MBSR) techniques, such as yoga, breath work, meditation, and mindfulness. Empowering patients to have the ability to change their perception of stress impact can help them cope with psoriasis [148]. Another commonly used methods of helping patients cope with the effects of stress include the use of adaptogenic herbs such as ashwagandha, rhodiola rosea, magnolia officinalis, phellodendron amurense bark and schizandra [149]. Adaptogenic herbs influence the chaperone proteins associated with glucocorticoid receptors thus altering the impact of cortisol.

Nutritional Supplements

"*Dietary supplementation in patients with psoriasis demonstrates consistent evidence supporting the efficacy of fish oil supplements. Zinc supplementation has not been shown to be effective; however, some evidence is available (albeit conflicting) for vitamin D, vitamin B12, and selenium supplementation*"

Talbot W [150]

There is compelling evidence to suggest that oxidative stress is involved in the pathogenesis of psoriasis [151]. Oxidative stress, being one of the stress stimulating triggers of PP, involves the presence of higher levels

of free radicals (including free reactive iron) in the skin along with reduced levels of potent antioxidants, serum super oxide dismutase (SOD) and glutathione peroxidase (GPX). This state, coupled with elevated levels of nitric oxide (NO), creates nitrosative stress which lead to cellular damage. Therapeutic use of iron chelators and antioxidants may have a beneficial role in PP for patients who have tested positive for high cellular damage marker thiobarbituric acid reacting substance (TBARS), total thiol, total antioxidant status (TAS), and ferritin [152].

Oral supplementation with the antioxidants coenzyme Q10, vitamin E, and selenium could also be feasible for the management of patients with severe forms of psoriasis [153]. Topical/transdermal formulations with antioxidants such as selenium, Co-Q10 and SOD are available through compounding.

Alternative Therapies

Alternative approaches are being used by PP patients. Complementary and alternative medicine (CAM) includes traditional Chinese medicine, herbal therapies, supplements, climatotherapy and mind/body interventions.

An herbal product, total glucosides of paeony (TGP) combined with acitretin, was evaluated in a randomized, double-blind, placebo-controlled, multi-center clinical study with 108 patients diagnosed with moderate-to-severe PP. They were randomly assigned to treatment

with "TGP plus acitretin" or "placebo plus acitretin" for 12 weeks. At the conclusion, the percentage of patients achieving a 50% reduction in the PASI was 90% in group A and 70.5% in group B ($p<0.05$). The rate of serum alanine aminotransferase elevation was 6.25% in the TGP plus acitretin group and 20.4% in placebo plus acitretin group ($p<0.05$). TGP is conducive to enhancing anti-psoriatic efficacy and reducing liver damage due to acitretin. The conclusion was that TGP combined with acitretin is a safe and effective treatment approach for moderate-to-severe plaque psoriasis. An important note is that the rate of serum alanine aminotransferase elevation was significantly less in the TGP plus acitretin group as compared to the acitretin only group [154].

Curcumin, the active polyphenol in turmeric, has anti-inflammatory effects that have been well documented in medical studies, with wide ranging applications from the treatment of rheumatologic diseases such as arthritis to dermatology, with significant effects in the treatment of psoriasis [155]. One disadvantage of topical use of curcumin is that it is a vivid yellow color and is not esthetically pleasing. There is a colorless chemical cousin, tetrahydro curcuminoid, but unfortunately the biologic activity is not the same. Oral dosing of a liposomal curcumin is preferred to enhance absorption.

Patients with psoriasis often use botanical therapies as part of their treatment and a recent review of oral use botanicals looked at the data from 12 studies and found evidence that HESA-A (a natural compound from herbal-marine origin), curcumin, neem extract (from India with apparent immunomodulatory and apoptotic effects) and, to a lesser degree, Traditional Chinese Medicine seem to be the most efficacious agents [156].

An additional review looked at 27 trials of topical botanical agents and found that the most highly studied and most efficacious topical botanical therapeutics were *mahonia aquifolium, indigo naturalis,* aloe vera, and, to a lesser degree, capsaicin [157].

Of the triggers previously discussed, bacterial infection, antibiotic treatment or profound changes in diet tell us that the gut microbiome is involved. In fact there is a close association between microbiota and psoriatic episodes [158]. Through the study of mouse models of inflammatory autoimmune diseases, gut microbiota have been shown to profoundly influence the immune system development and reactivity [159]. There is evidence that the course of certain autoimmune diseases in humans can be altered with antibiotics and probiotics and by restricting the complexity of the microbiota [160]. Studies show improvement for several dermatologic conditions, including psoriasis, with the treatment of certain probiotics [161].

There is also evidence that the cutaneous microbiome of PP patients differs from healthy controls.However, at the present time, there are no products designed to take advantage of this potential avenue of therapy,[162] unlike the gut microbiome for which probiotics are currently used to treat gut microflora disruption. Prebiotics and/or probiotics have a positive effect on skin by modulating the immune system [163].

Pregnancy Considerations for Treatment of PP

In a recent article by the Australasian College of Dermatologists, the following general recommendation was made: "Effective drugs that have been widely used for years are preferable to newer alternatives with less fetal safety data. It is equally important to evaluate the risks of not treating, as severe untreated disease may negatively impact both mother and the fetus" [164].

UVB can be safely used in the treatment of a pregnant woman with psoriasis, and the risk of topical PUVA is considered low in pregnancy. Adalimumab, etanercept, and infliximab come under FDA category B: animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women. Anthralin, betamethasone dipropionate, calcineurin inhibitors, cyclosporine, psoralen, and methylprednisolone aceptonate are category C drugs:

animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

Acitretin, methotrexate and tazarotene belong to category X: studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits [165,166]. Therefore these drugs must not be given to any female of reproductive potential until pregnancy has been excluded. Additionally, the manufacturers of acitretin have established a Pregnancy Prevention Actively Required During and After Treatment campaign, designed to help prevent pregnancies from occurring during and for 3 years after treatment.

The FDA published (12/3/14) the Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling, referred to as the "Pregnancy and Lactation Labeling Rule" (PLLR or final rule). Once fully implemented it will remove the pregnancy letter categories – A, B, C, D and X. The PLLR also requires the label to be updated when information becomes outdated. Prescription drugs and biologic products submitted after June 30, 2015, are using the new format, while labeling for prescription drugs approved on or after June 30, 2001, will be phased in

gradually. The definitions of the categories were included here for accuracy of understanding [167].

Conclusions

In patients with PP in the absence of PsA the AAD psoriasis clinical guidelines advocate using topical agents and/or targeted phototherapy for limited disease. For extensive disease, when there is a lack of effect from topical agents and/or phototherapy, the guidelines recommend to use UVB/PUVA. If there is a lack of effect from UVB/PUVA then use systemic medications and if there is a lack of effect with that then move to biologics. The guidelines offer no guarantee of success, also the ultimate decisions of therapy must be patient determined by the clinician [168]. The current consensus of therapy continues to reflect these guideline recommendations.However, changing the patient's diet and lifestyle that contribute to the etiology and progression must also be addressed to change the course of the disease and the potential for comorbidities.

There is no perfect treatment for PP. From the information presented here it is clear that there are pros and cons to all forms of treatment. Understanding the treatment options allows the clinician to modulate and adjust therapy to fit each patient while minimizing AEs. If the clinician starts simple and progressively, uses the above mentioned guidelines combining treatments when appropriate, there is a reasonably good opportunity to improve the appearance and QOL for a majority of patients.

Opinion

Biological drugs are promising, innovative and new. They are efficacious in many instances but they have very different side effect profiles as compared to the more conventional therapies. The AEs of systemic agents like MTX, cyclosporine and acitretin can also be serious however all of the biological drugs have black box warnings of the potential for severe infections and malignancy. This along with the uncertainty of their long-term effects on the immune system and their expense should put them last on the list of treatment options.

As a trigger and a sustaining source of inflammation, diet matters and has major implications in the treatment of PP. Clinicians must take a holistic approach to treatment, encouraging patients to decrease intake of proflammatory foods and other substances that contribute to inflammation. To do otherwise is to practice myopic medicine.

While every source of medical information is likely to have bias, we must strive to look towards keeping an open mind and helping the patient in the best way possible, given their resources and access to the various treatment options. This should start with trying to treat the cause of the disease and not just the symptoms or biomarkers. A lot of patients are motivated to change but not every patient is ready (or capable) to make lifestyle changes needed to correct the cause so it is important to "meet them at their level", and if nothing else plant seeds for the future and hope they find value in change with positive impact at some point.

One last note regarding this topic, is that the volume of information published about PP is massive and growing at an impressive rate. It was impossible to present all relevant information in this monograph. As is true of all scientific publications, this one is already be out of date as you read it, so don't stop here with your education, follow the evolution of the data as we continue to uncover more knowledge in the quest to help our patients who have entrusted us with their care.

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