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Psoriasis

Adolfo Fernandez-Obregon
Hoboken
USA

1. Introduction

Psoriasis is a common, chronic inflammatory and proliferative condition of the skin, sometimes affecting joints, in which both genetic and environmental influences play a critical role. Most characteristically, it consists of scaly, sharply demarcated red and indurated plaques, present particularly over extensor surfaces sometimes overlying the joints, and occasionally involving the scalp.

2. Epidemiology

Psoriasis affects between 2% and 3% of people worldwide. [1] This varies from an incidence of 1.5% to 4.8% in Northern Europe [2] to China, where the lower prevalence of 0.3% has been observed. [3] Nearly one quarter of these have moderate to severe psoriasis consistent with involvement of >3% of body surface area. Women (OR = 1.37, 95% CI: 1.14–1.64) are slightly more likely than men and African Americans less likely than Caucasians (OR = 0.54; 95% CI: 0.34–0.85) to report a psoriasis diagnosis. [4]

Psoriasis can develop at any age, but symptoms typically first appear between ages 15 and 25 years. Approximately one half of patients diagnosed with psoriasis report suffering with pruritus. [5] In a large US survey, the average age of onset was 28 years, while in China it was 36. In other studies, both sexes appear to be equally affected. Table 1 shows world-wide studies on prevalence of psoriasis.

Looking at the white population in Rochester, MN, Bell *et al* reported an incidence of 60.4 per 100,000 adjusted for sex and age, during the 1980 Rochester Epidemiology Project. [6] From the same project Shbeeb *et al* looked at the population from 1982 and 1991 and reported a rising incidence to 107.7 per 100,000. [7] Those same increasing trends were confirmed by similar studies by Icen *et al* in the same population, and by Huerta *et al* looking at the population in the United Kingdom. [8] [9] The reasons for this increase cannot be explained alone on known genetic factors. Other environmental influences or unknown genetic factors may play a role in this observation. The lack of obvious family history in many cases of newly diagnosed disease underscores this concept.

3. Genetic & environmental causes

3.1 Genetic basis of psoriasis

A search for the genetic basis of psoriasis has been seriously undertaken by Gunnar Lomholt who studied heredity in residents of the Faroe Islands. Farber and Nall subsequently

studied the concordance rates in monozygotic twins and documented kindreds having multiple family members afflicted with the diseases. [10] [11] Population studies revealed a higher incidence of psoriasis among first- and second-degree relatives than in the general population. However, just as the pathogenesis is complex, the mode of inheritance is also complex. Of nine distinct chromosomal loci, 7 of which have been clearly identified as being associated with psoriasis.

World Region & Reference	Prevalence (%)
Europe	
Norway	1.4-4.8
Sweden	2.3
Denmark 28	2;5-3.2
United Kingdom 28	1.5-2.8
Croatia 28	1.55
Italy	0.8-4.5
Germany	2.5-3.5
France	3.58-5.2
Spain	1.43
Czechoslovakia 28	1.2
Hungary 28	2.0
Netherlands 28	1.8
New World	
North America 28	0.5 – 4.7
African-Americans	1.3
Newfoundland, Canada	2-3
South America 28 28	0.2-4.2
Caribbean 28 28	1.3-6.0
Africa	
West Africa 28	0.05-0.9
East Africa 28	2.8-3.5
North Africa 28	3.0
South Africa 28	1.5
Oceania	
Australian Aborigines	0.47
Australian Caucasians	2.3-2.57
Samoa Islands 28	0
Asia	
China 28 28	0.05-1.23
Japan 28	0.29-1.18
India 28	0.5-2.3
Malaysia 28	1.1-5.5

Table 1. Worldwide Prevalence of Psoriasis

The most important genetic determinant of psoriasis is PSORS1 (psoriasis susceptibility locus), widely considered to be a susceptibility locus for the development of psoriasis accounting probably for 35 to 50% of the heritability of the disease. [12] PSORS1 is found within the major histocompatibility complex (MHC) on chromosome 6p. Identification of the specific gene has been difficult because of the extensive linkage disequilibrium observed within the MHC. There are 3 genes within this locus that are strongly associated with inheriting the disease. [13] [14] These genes code proteins that may be over-expressed in psoriasis.[15] Others are found are exclusively found in the granular and cornified layers of the epidermis. [16] Studies show variants of psoriasis may be genetically heterogeneous. Guttate psoriasis appears to be strongly associated with PSORS1, [17] as opposed to late onset cases of psoriasis, generally occurring in persons over 50 years of age. [18]

Genetic Marker	**Chromosome Location**	**Function**	**Associated Diseases**
PSOR 1 54, 55 [19]	6p	HLA-CW6 & corneodesmposin	?
PSOR 2 62	17q	Immune synapse	?
IL12B 63, 64 [20]	5q	T-cell differentiation	Crohn's Disease
IL23R 55, 68, 69, [21] [22]	1p	T-cell differentiation	Crohn's Disease, ankylosing spondylitis, psoriatic arthritis, type I diabetes, celiac disease
ZNF 313 (RNF114) 55 69	20q	Ubiquitin pathway	?
CDKAL1 [23] [24]	6p	?	Crohn's Disease, type 2 diabetes mellitus
PTPN22 75, [25] [26]	6p	T cell signaling	Type 1 diabetes mellitus, juvenile idiopathic arthritis, systemic lupus erythematosus, rheumatoid arthritis, autoimmune thyroid disease
IL-4 – IL-13 cytokine gene cluster 55 [27]	5q	T-cell differentiation	Crohn's Disease (variant)
LCE3B/3C 66 [28]	1q	Epidermal differentiation	

Table 2. Genetic Markers associated with Psoriasis

PSORS2 is the second gene locus found associated with psoriasis. [29] Two genes in this region, SLC9A3R1 and NAT9, reside in chromosome 17q24-q25. [30] They contribute to the immunopathogenesis of psoriasis through their role on immunological synapse. This refers to the signaling accomplished by multimolecular complex formation between the mature T cell through its receptor (TCR), and the antigen presenting cell (APC). Through a series of adhesion molecules, like LFA-1, T cells can bind to ICAM-1 expressed in an adjacent cell like a keratinocyte or APC. The LFA-1 component was found particularly useful in therapy. By blocking this adhesion interaction, efalizumab was used to treat psoriasis. [31] Other adhesion molecules exist, and have been evaluated for a possible role in defining hereditary patterns of psoriasis and targeting these processes for therapy. For instance, LFA-3 Ig fusion protein (alefacept) has been found to reduce psoriasis lesions.[32]

Additional findings suggest LCE3B/3C, located within the epidermal differentiation complex on chromosome 1, is also strongly associated with the development of psoriasis. [33] Deletion of these genes is associated with a significant fraction in individuals of European ancestry with psoriasis. [34] Other genes that have been linked to psoriasis include ZNF313 (allele RNF114), which plays a role in the ubiquitin pathway, and CDKAL1, the function of which is not known at this time. [35] PTPN22 plays a role in T cell signaling. Other associations involve variants of the gene encoding the IL-23 receptor (IL-23R) and a region of the IL-12B (p40) gene as being closely linked to risk for psoriasis. IL-23R also appears in association with psoriatic arthritis and ankylosing spondylitis. CDKAL1 shows association with psoriasis and Crohn's disease, and type 2 diabetes mellitus. [36] [37] Nearly all of the genes listed are associated with the immune response strongly implicating an immunologic basis for the pathogenesis of psoriasis.

3.2 Environmental causes of psoriasis

As with many other diseases, there are interactions between genetic factors and the environment. Psoriatic lesions appearing at the site of injury are a well known phenomenon (Koebner or isomorphic response). This injury can be a physical, chemical, electrical, infective, sun-burn or other inflammatory insult. The reverse Koebner phenomenon has also been observed to occur and refers to clearing of psoriasis after an injury or illness. [38]

Streptococcal infection has been shown to precede the onset of guttate psoriasis, especially in those with a family history of plaque psoriasis, and drugs have been implicated as an initial cause or exacerbating bouts of psoriasis. [39] Among these are lithium salts, antimalarials, beta-adrenergic blocking agents, non-steroidal anti-inflammatory drugs, angiotensin converting enzyme inhibitors, and the sudden withdrawal of corticosteroids. [40]

Other factors that may play a role include pregnancy, [41] alcohol, smoking, [42] psychogenic stress factors [43] and concomitant HIV disease and acquired immune deficiency. [44]

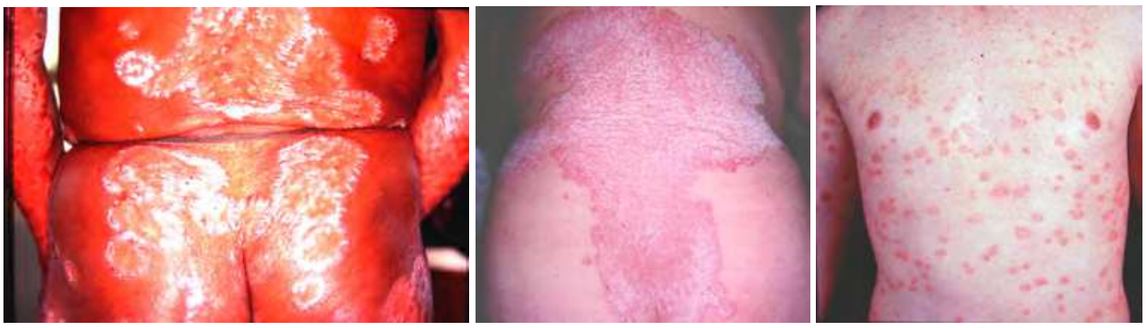
4. Psycho-social considerations

Many patients with psoriasis, particularly those with severe disease, are frustrated with the management of their disease and the ineffectiveness of their therapies. A National Psoriasis Foundation (NPF) survey looking at a large number of patients revealed individuals suffering with psoriasis want to communicate their frustrations about their disease, and the disappointment about their treatments.[45]

Other studies reported that psoriasis sufferers experience difficulties in the workplace and in socialization with family members and friends, exclusion from public facilities, difficulties obtaining a job, and even contemplation of suicide. Other opinions expressed included feeling embarrassed, unattractive and depressed. The disease process was often described as a large problem in everyday life, influencing the choice of clothing used to cover psoriasis. Many claimed psoriasis interfered with their ability to sleep, and interfered with their sexual activities. About one third of those evaluated claimed having problems using their hands, walking, sitting, or standing for prolonged periods. [46] Another study reported 48% of respondents were not working, 20% of whom attributed their unemployment to their psoriasis or psoriatic arthritis. [47]

5. Clinical presentation – Subtypes of psoriasis (adults & children)

Psoriasis most commonly presents as the chronic stable large plaque disorder commonly referred to as psoriasis vulgaris. The scales are silvery and have been described as "micaceous" on an underlying salmon pink in color. The thickened epidermis allows the cutaneous vessels to come very close to the scaly *stratum corneum*. Dislodging the scale in essence causes a tear in the epidermis resulting in bleeding, known as the Auspitz sign. Psoriasis plaques are characterized by thickened silvery white scales on a red base of skin. Lesions may occur as a few small plaques or become more widespread throughout the body. [48] In one survey, the most frequent symptoms experienced were scaling, itching, skin redness, lightness of the skin, bleeding at lesion sites, burning sensation, and fatigue. [49]



a) b)

Fig. 1. a) Large Chronic Plaque Psoriasis in an obese Caucasian and in a member of the Choclo natives of Southern Panama, with extensive plaques in spite of an outdoor life style while wearing minimal clothing. b) Guttate Psoriasis

A ring of hypopigmented normal skin often surrounds the psoriatic plaque, commonly referred o as the Woronoff ring. [50] Customarily it appears as the skin tries to repair itself, an has been used as an indication therapy is working. [51] [52]

Guttate psoriasis describes a "shower" of smaller less scaly and erythematous lesions appearing in a widespread to generalized distribution. They occur less commonly on the face. This variant occurs more commonly in children and young adults, often secondary to an acute infection, usually streptococcal.

Erythrodermic psoriasis results when chronic lesions evolve and coalesce into a generalized exfoliative phase. In this scenario it behaves either like an extensive form of large plaque

psoriasis, which generally responds to therapy, or as the "unstable" form of psoriasis which can result from discontinuation of systemic corticosteroids, [53] Not commonly it can seen with joint involvement, or as the end result of a generalized pustular psoriasis. Individuals with this form tend to be febrile, highly resistant to tolerating any topical regimen, or phototherapy, and can present with metabolic complications related to sweating imbalance leading to abnormal thermoregulation, electrolyte abnormalities, intestinal absorption, and negative protein balance. [54] [55] [56]

Histological changes of psoriasis (hematoxylin and eosin), from a punch biopsy of a large plque, shows epidermal thickening with parakeratosis, and elongation of the rete ridges with mixed cellular infiltrate – T-cells an polymorphonuclear neutrophils (PMN). Vascular dilatation, and microabscesses (Munroe) with PMN form with disease progression.

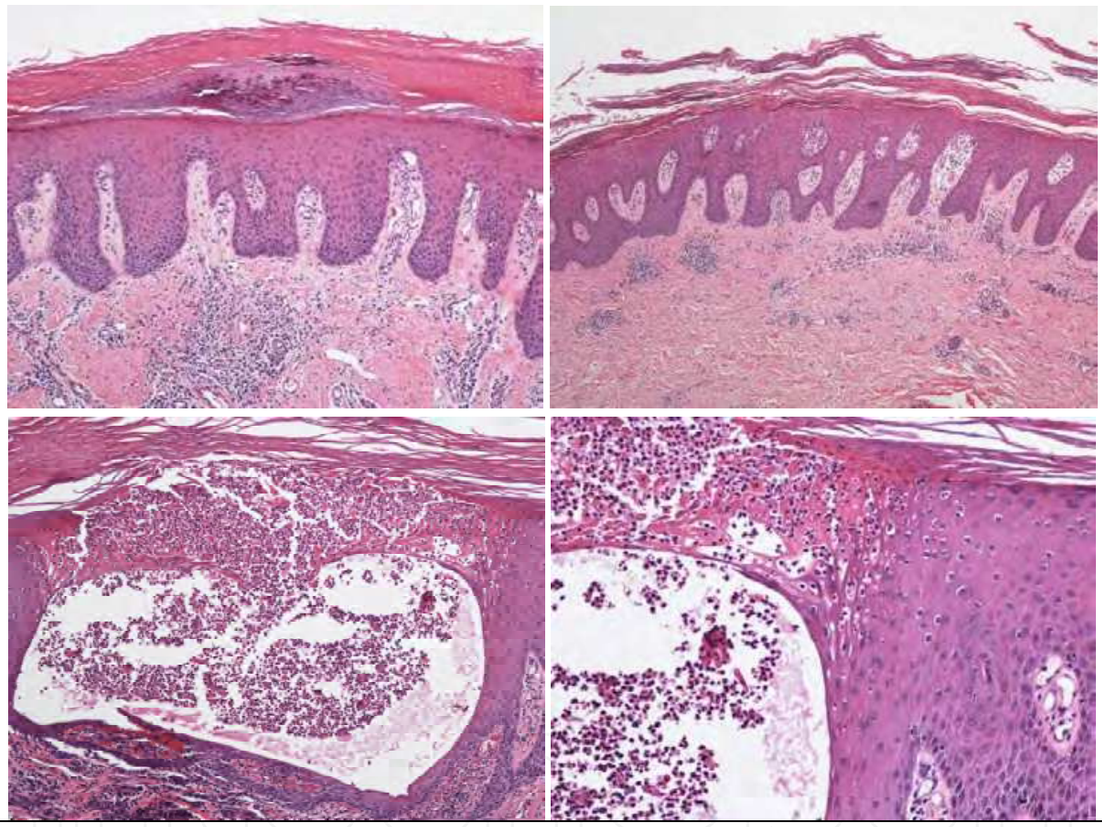


Fig. 2. Histologic Features of Psoriasis

Another manner to categorize psoriasis involves the anatomical distribution. Scalp psoriasis can be a part of large plaque psoriasis. Often it is seen as the sole anatomic area involved in the skin, presenting a therapeutic challenge due to the very thick nature of the plaques that form.

Genital involvement in males and females may occur as part of widespread disease or as a sole manifestation involving the glans mimicking erythroplasia or Zoon's balanitis. Sometimes, it can also occur on the flexural surface of the groins and vulva as part of inverse psoriasis, which can also exist on the axillas, submammary, gluteal cleft and other body folds. This is more common in older adults. Scaling is greatly reduced. Failure of these eruptions to respond to suspected fungal or yeast infections should raise suspicion.

Hands and feet may occur as well-defined plaques resembling hyperkeratotic eczema (palmo-plantar plaque psoriasis), or as a pustulosis, (palmo-plantar pustular psoriasis) or as a mixture of the two. It can be seen in connection with occupational use of irritants. [57]

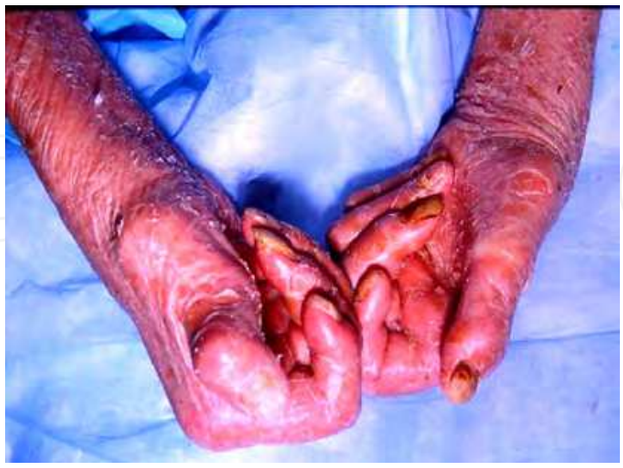


Fig. 3. Erythrodermic psoriasis & psoriatic arthritis with chronic joint deformity

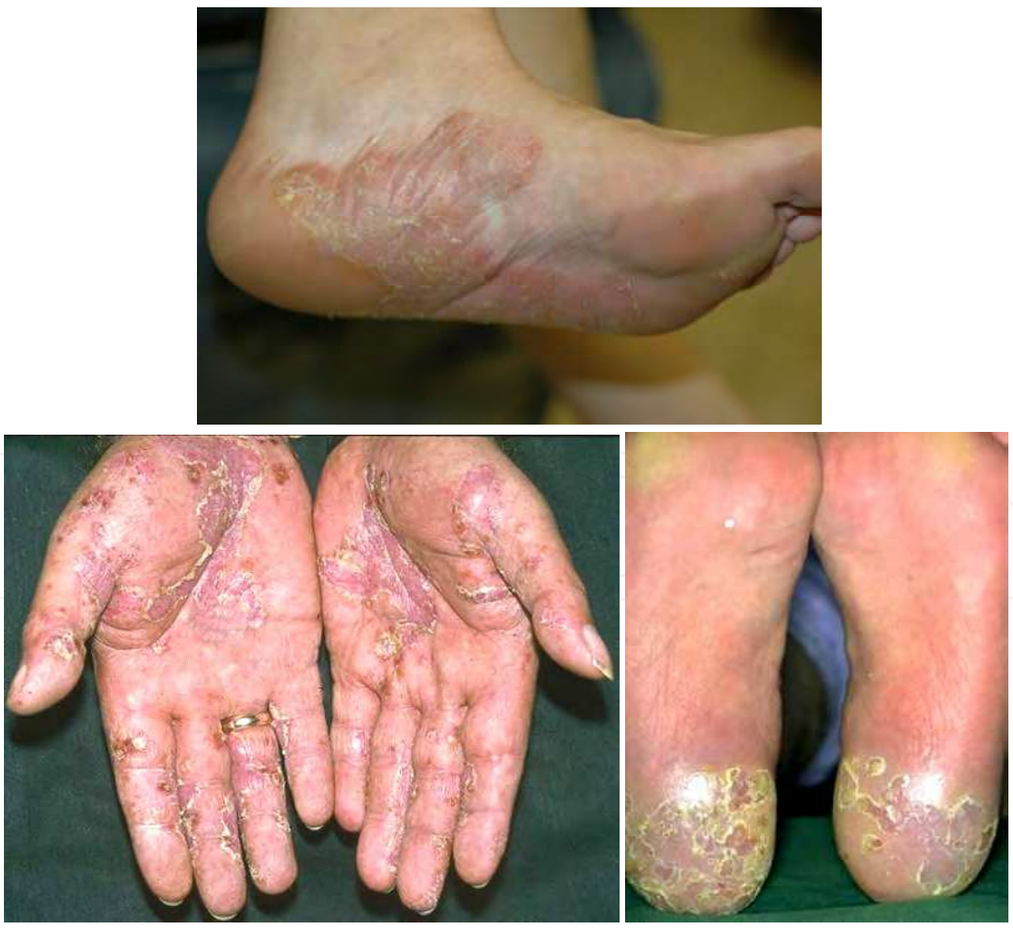


Fig. 4. Palmoplantar Plaque Psoriasis

Nail involvement can be seen in association with all types of psoriasis. It can be a predictor of psoriatic arthropathy, and as such is often seen in psoriatic patients with psoriatic arthritis. [58] Although pitting is the most frequent change seen, discoloration, subungual hyperkeratosis, and onycholysis are common. Splinter hemorrhages can occur. Nail disease is more severe in familial cases and when disease onset is early. Patients over 40 years of age are twice as affected as those under 20. [59] Longitudinal biopsy of the nail bed and matrix studies have shed some light on the cause of these changes. [60] Nail pits, ridges and grooves result from psoriasis of the nail matrix, whereas onycholysis, subungual hyperkeratosis, and splinter hemorrhages are attributable to disease of the nail bed or hyponychium. [61] Circular discoloration of the nail bed and hyponychium may resemble an "oil drop" below the nail. This observation represents histologically psoriatic change in the hyponychium. [62] Candidal onychomycosis is a common find in psoriatic nails, but dermatophytes are rare. [63]

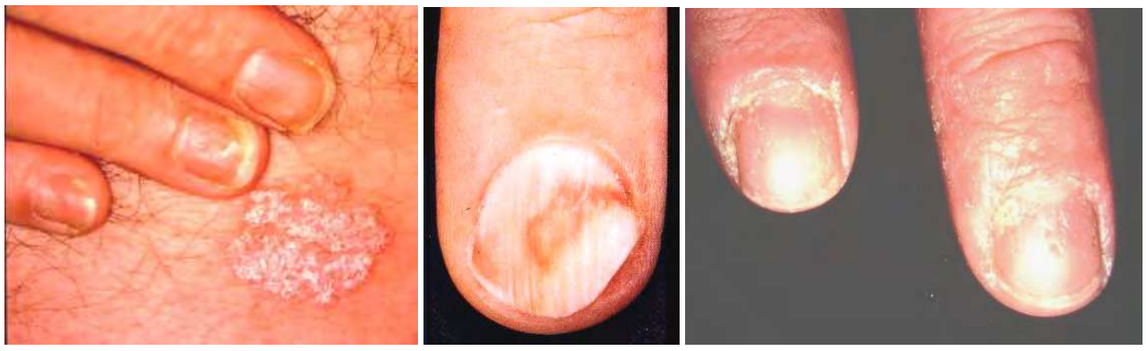


Fig. 5. Nail changes in Psoriasis

5.1 Psoriasis in children

Psoriasis occurs approximately 1/3 of the time during the first two decades of life, and is therefore quite common in children. [64] Guttate psoriasis is frequently seen in children. Inverse psoriasis can present in the form of a toe cleft intertrigo, a chronic blepharitis, or perleche on the angle of the mouth or a lateral eye lid. Psoriasis on the face occurs more often in children than in adults. Scalp involvement and a psoriatic rash in the napkin area are common.

5.2 Differential diagnosis

The rash of eczema, at times, can present with a psoriasiform appearance. As mentioned previously, psoriasis of the hands can appear indistinguishable from contact dermatitis, since irritants can often exacerbate or herald onset of activity. Lichen planus (LP) can at times have a dusky red presentation similar to early psoriasis. LP can also coexist with psoriasis. When involving skin close to the elbows, knees or shins, lichen simplex can mimic psoriasis. Pityriasis lichenoides chronica or Muccha-Habermann Disease, can appear like guttate psoriasis. Skin biopsy is sometimes necessary to differentiate these entities. Candidiasis, particularly in the flexural areas has been mistaken for psoriasis. Dermatophytosis is generally differentiated from psoriasis by the nature of the scale that spreads over the expanding margins. Pityriasis rubra pilaris and secondary syphilis can be confused with erythroderma. Lymphoma of the skin, and toxic erythema caused by drugs

can present similarly with an erythrodermic presentation. Psoriasis cutaneous lymphoma, and leprosy are three clinical entities that can typically present with secondary lesions that have "skip areas." This refers to islands of normal skin appearing within the lesion.

5.3 Psoriatic arthritis

Psoriatic arthritis (PsA) is inflammatory in nature. These patients tend to present with pain, stiffness, and swelling of affected joints. [65] Up to 30% of psoriatic patients have PsA, a progressive and destructive disease. Psoriatic arthritis usually develops between 30-50 years of age. Generally, skin symptoms appear earlier than joint symptoms (70% of cases). Likelihood of developing PsA may also correlate with duration and severity of psoriasis. However, in 15 % of patients, the joint manifestations may appear before the skin changes by as many as 10-15 years. In the remaining 15% the skin and joint symptoms appear simultaneously. Sensitizing clinicians to the morbidity of these diseases may aid in optimizing psoriasis management and patient care. [66] [67] [68] [69] [70] Nail involvement is observed in 70-80% of these patients making this clinical observation a valuable predictive clinical sign for the development of PsA. 28 [71] Severity of nail disease correlates with severity of skin disease. As early as 2008, the American Academy of Dermatology (AAD) issued guidelines for the management of psoriasis and psoriatic arthritis. The most commonly affected joints were listed to be those in the wrist, knees, ankles, lower back, and neck. [72]

Prolonged morning stiffness, lasting longer than 60 minutes, is a common complaint, and results from inflammatory involvement of entheses, the point at which tendons or ligaments insert to bone. It tends to improve throughout the day. What begins as oligoarthritis (4 or less joints) may progress to polyarticular (more than 4 joints) over years, and may revert back to oligoarthritis with treatment. Though patterns of presentation are not helpful to identify PsA, the distal inter-phalangeal joint (DIP) may be the most readily recognizable because it is unique to PsA. It occurs in 5%-10% of patients and is seen predominantly in men. An asymmetric oligoarthritis occurs in 30% of cases, a large joint is generally involved like a knee, in association with a few small joints of the hands and feet, commonly with dactylitis. The polyarthritis pattern, practically as common, is seen more often in women, it involves fingers, wrists, toes and ankles. It involves DIP joints and is asymmetric. In comparison with RA, in PsA all joints of one digit tend to be involved while sparing other digits, whereas in RA the same joint is involved in all the digits. Whereas synovitis is the primary lesion of rheumatoid arthritis (RA), synovitis along with enthesitis characterizes PsA. [73] The most common sites of entheseal involvement in PsA include the attachment of the Achilles tendon or the plantar fascia to the calcaneus, as well as the ligaments around the rib cage, pelvis, vertebral bodies, posterior tibial tendon, quadriceps muscle, patellar tendon, and the elbow.

Arthritis mutilans of hands and feet occurs infrequently, about 5% of the times. Axial disease, when it occurs alone, is equally infrequent and is seen in 5% of cases. More commonly, it is seen in association with peripheral arthritis. About 40% of patients in general have some form of axial disease. The cervical pine is involved more frequently than the thoraco-lumbar. [74]

Constitutional symptoms associated with PsA are similar to those observed in other types of inflammatory arthritis, and include fatigue, anorexia, weight loss and general weakness. Conjunctivitis and or uveitis (pain, lacrimation and photophobia) may present in up to 1/3 of cases. It tends to be chronic and bilateral.

5.3.1 Physical examination

Proper evaluation requires an examination of all joints; this includes the feet, which often reveal significant pathology. Erythema overlying the joints, and often over the distal phalanges is often seen in hands as well as feet. Selling of the second and third metacarpo-phalangeal joint of the hands may be prominent. Swelling of the large joints like the knees may be noted as well. Dactylitis or fusiform swelling of the digits or toes is the result of inflammation of the phalangeal joints along with enthesitis. Mutilating psoriatic arthritis can result with shortening of the fingers opera (opera glass or telescoping effect).

5.3.2 Laboratory & imaging studies

There is no specific serologic marker for PsA. Though acute phase reactants like CRP, and ESR may be elevated, they are far from specific. HLAB27 is not much better in specificity. While it may appear in 50%-70% of sufferer with axial disease, and less than 15% of those with peripheral disease, it may appear in 7% of normal North American Caucasians, and its presence is independent of disease severity. [75]

Imaging findings center on visualizing radiographic evidence of new bone proliferation or periostitis observed adjacent to erosions, and at sites of entheseal attachments. Marginal erosions of bones may progress to involve the central articular surface resulting in the characteristic "pencil in cup" finding. This progressive loss of bone results in collapse of the phalanges and metacarpal bone resulting in the opera glass or telescoping deformity. MRI and ultrasound are of greater value than plain radiographic film when evaluating the presence of enthesitis. [76] Rheumatoid Factor (RF) may help confirm the diagnosis of RA (at least in 2/3 of the cases); however, RF is positive in 5% of adults, increasing in frequency with age, so that 20% of those over 65 years of age may have a positive RF. In patients with PsA, RF may be positive 5%-10% of the time. Even antibodies to citrullinated-containing proteins (AntiCCP) with improved sensitivity and specificity over RF for RA, are positive in PsA in less than 7%. [77]

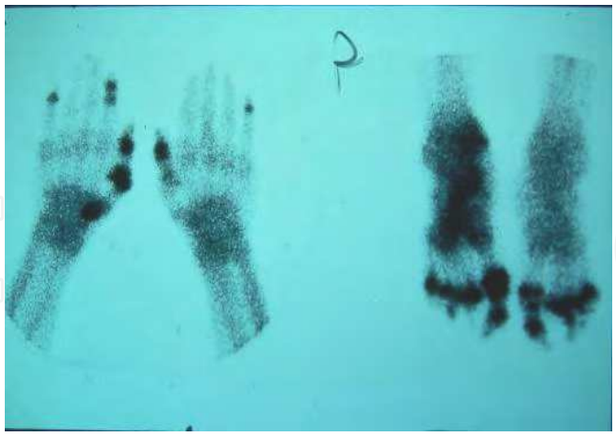


Fig. 6. Nuclear scan of hands and feet - in a psoriatic patient showing asymmetric uptake of radiolabeled Technitium-99 material taken up by inflamed joints

5.3.3 Classification of psoriatic arthritis

Two types of classification (Moll & Wright and CASPAR) are commonly used to categorize psoriatic arthritis. It is often helpful to use one of these when describing clinical severity.

This exercise is useful when seeking approval for systemic therapy from government or private insurance carriers. According to the AAD, the Moll and Wright criteria for classifying psoriatic arthritis, developed in 1973, are frequently used. The Moll & Wright Classification criteria have a specificity of 98% and a sensitivity of 91%.

To meet the Moll and Wright classification criteria, a patient must present with psoriasis, and seronegative inflammatory arthritis with one of several different criteria including:

- Polyarticular, symmetric arthritis (rheumatoid arthritis-like)
- Oligoarticular (< 5 joints), asymmetric arthritis
- Distal interphalangeal joint predominant
- Spondylitis predominant
- *Arthritis mutilans*

The CASPAR (classification criteria for psoriatic arthritis) criteria consist of established inflammatory arthritis defined by the presence of tender and swollen joints and prolonged morning- or immobility-induced stiffness with at least 3 points from the following features1,2:

- Current psoriasis (assigned a score of 2; all other features are assigned a score of 1)
- A personal history of psoriasis (unless current psoriasis is present)
- A family history of psoriasis (unless current psoriasis is present or there is a personal history of psoriasis)
- Current dactylitis or history of dactylitis recorded by a rheumatologist
- Juxtaarticular new bone formation
- Rheumatoid factor negativity
- Typical psoriasis nail dystrophy including onycholysis, pitting, and hyperkeratosis

The CASPAR criteria have a specificity of 99% and a sensitivity of 91%. 28 28

5.4 Psoriasis Area and Severity Index (PASI) & its role in clinical research

Psoriasis Area and Severity Index (PASI) score provides a means of assessing psoriasis that takes into account both the severity and extent of disease. The PASI score for an individual patient is calculated by adding the scores of the four body regions: the head, the trunk, the arms, and the legs. It ranges from 0 to 72. [78] The score for a single region is obtained by multiplying the percentage of surface area occupied by the region (e.g., 0.1 for the head) times the degree of involvement for that region, assessed on a scale of 0 to 6. The result is multiplied by the overall severity score for the region, defined as the sum of scores for redness, thickness, and scale, calculated on a scale of 0 to 4. The resultant scores are then added for each body region to yield the overall PASI score. The PASI has become a tool for measuring disease severity and evaluating how a therapeutic agent lowers the subject's score.

One problem with this index is that it presumes the area of involvement corresponds with severity of disease. It would be possible for a patient with thick plaques on the scalp, elbows and knees to have the same score as one having minimal plaques in the arms and trunk. The former would pose a therapeutic challenge in comparison with the latter, yet their index scores would fail to capture this discrepancy.

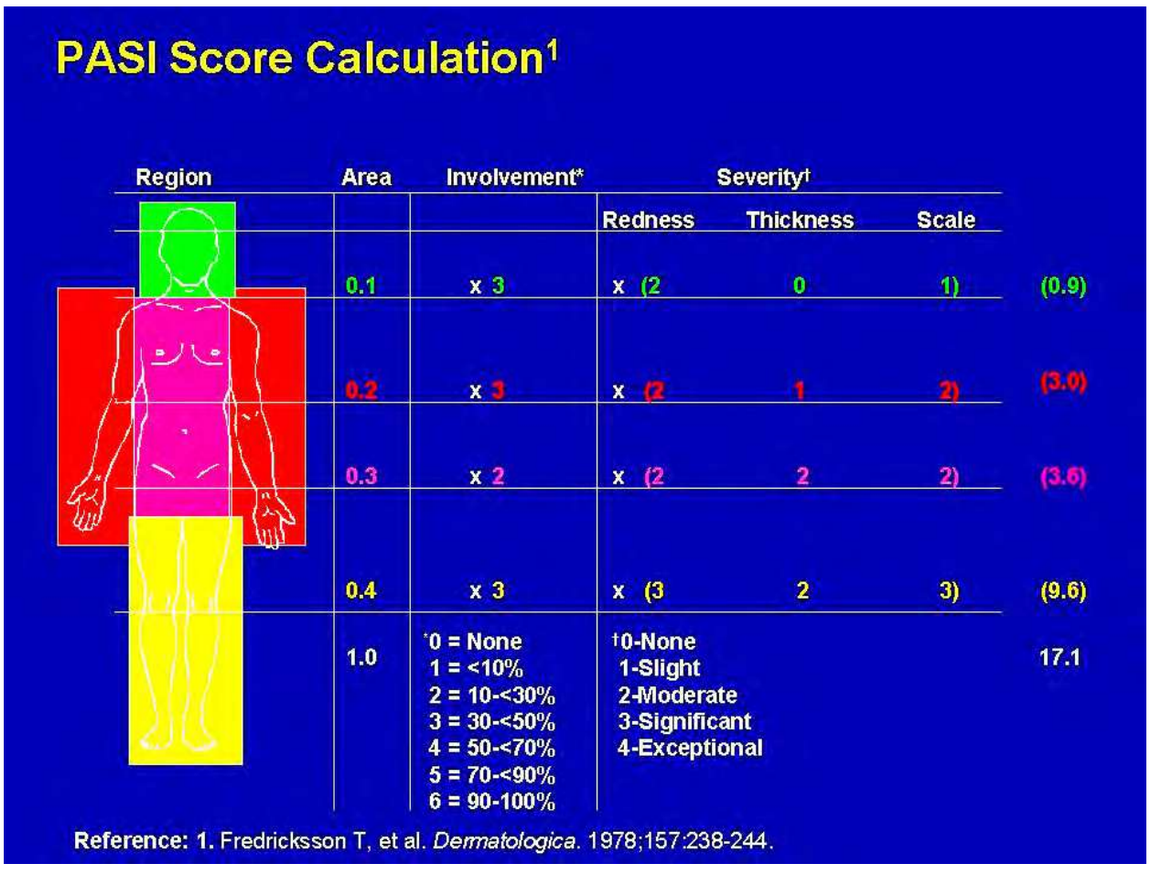


Fig. 7. PASI Score scale. In the example shown here, the score for the trunk is obtained by multiplying 0.3 x 2 x the sum of 2 + 2 + 2, to yield a score of 3.6. When the scores for the four regions are added, we get a PASI Score of 17.1.

Other indices used to categorize disease severity include body surface area (BSA), dermatology life quality index (DQLI), .[79] and the global physician assessment (GPA). [80]

Puzenat *et al* studies a group of indices used to evaluate psoriasis severity. Based on this systematic review, it appears that none of the severity scores used for psoriasis meets all of the validation criteria required for an ideal score. However, we can conclude that the PASI score is the most extensively studied psoriasis clinical severity score and the most thoroughly validated according to methodological validation criteria. Despite certain limitations, use of the PASI score can be recommended for scientific evaluation of the clinical severity of psoriasis. [81]

6. Immunopathophysiology

The cytokine networking theory for the cause of psoriasis was postulated 20 years ago. [82] Proponents maintain that cytokines rather than non-protein type mediators like eicosanoids, orchestrate the multicellular conspiracy among immunocytes such as dentritic cells and T-cells as well as the cross talk between immunocytes and epidermal keratinocytes that culminates in the formation of the psoriatic plaque. There is mounting evidence the innate

immune system, by carrying out its intended role of providing an early response mechanism against harm to the host through its nonspecific effectors, may also help induce psoriasis. [83] Plasmacytoid dentritic cells, the foremost producers of interferon-α, a documented inducer of psoriasis,[84] are activated and increased in psoriatic lesions through complexes of the antimicrobial peptide LL37 (*cathelicidin)* and DNA in a toll-like receptor (TLR) 9 – dependent manner. [85] This provides a possible explanation of the mechanism by which host DNA is turned into a proinflammatory stimulus that breaks the immunologic tolerance in psoriasis.

Psoriatic keratinocytes are a rich source of antimicrobial peptides, including IL37, β-*defensins*, and S100A7 (*psoriasin*). These antimicrobial peptides also have strong chemotactic properties, and can help direct other cell functions in dendritic cells and T-cells. In addition, keratinocytes have a potential accessory role in skin immune response. They respond to cytokines derived from dendritic cells and T-cells including interferons, TNF, IL-17, & the IL-20 family of cytokines. They can also produce proinflammatory cytokines like IL-1, IL-6, TNF- α, and chemokines like IL-8 (CXCL*), CXCL10, and CCL20. (see Figure 1)

Dendritic cells bridge the gap between innate and adaptive immunity. Myeloid dermal dendritic cells are increased in psoriatic lesions and induce autoproliferation of T-cells and T_H1 cells. [86] A specialized subgroup (TIP dendritic cells) produce TNF- α, and inducible nitric oxide synthetase. [87] Targeted immunotherapy and psoralen and ultraviolet A (PUVA) therapy reduce the number of dendritic cells in psoriatic patients, adding validity to the role these cells play in the pathogenesis of psoriasis.[88] Clearly, it becomes evident the psoriatic inflammatory response is shaped by a complex interface between elements of the innate and the adaptive immune response. [89]

In two different studies, Zheng *et al* [90] and Chan [91] give IL-23 a potential role in the pathogenesis of psoriasis. Injecting IL-12 into mice skin leads to increased IFN-γ, whereas IL-23 injections increased production of other cytokines including IL-17 and IL-22, but not INF-γ. The traditional belief has been to categorize IL-12 and IFN-γ producing immunocytes as T_H1 type, promoting a cell-mediated immune response to intracellular pathogens. In contrast, T cells producing another collection of cytokines such as IL-4, IL-5, and IL-13 promote a humoral or antibody response to combat extracellular pathogens in a classical T_H2 type reaction. A new cytokine network has been identified belonging to the $CD4^+$ subset producing a different set of cytokines. This third effector cell is the T_H17, and it is directed by IL-23 with help from transforming growth factor (TGF-β) and IL-7 [92] It is apparent that through the promotion of T_H17 cells, IL-23 can play a role in the clearance of infections agents, but has the ability of mediating autoimmune inflammatory disease such as psoriasis and Crohn's Disease. These T_H17 cells produce IL-22, which is responsible for the epidermal thickening seen on psoriasis, and the production of antimicrobial peptides as well as chemokines (including Il-17, and Il-22). 28 It is believed this may be accomplished through the phosphorilation of Sta3, which has been found elevated in psoriatic plaques. [93] IL-22 also mediates the keratinocyte production of *defensins* & other molecules (antimicrobial cytokines) that help enhance the mobility and amplification of the inflammatory response leading to the phenotype of psoriasis [94] [95] With successful anti-TNF treatment, T_H17 cells are reduced, adding still further support to their functional role in psoriasis. [96] Figure 1 illustrates how targeting specific focal points responsible for the pathogenesis of psoriasis may lead to effective prevention of disease and its progression.

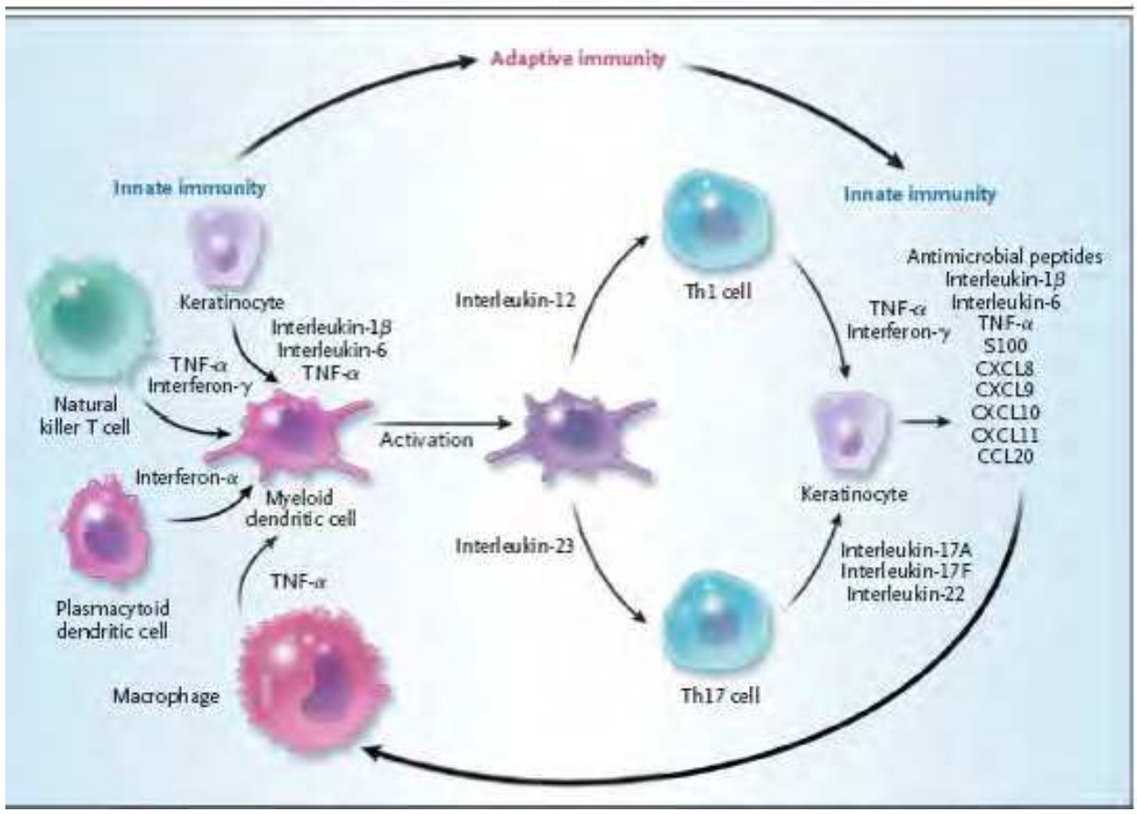


Fig. 8. Key Cells & Mediators in the transition from innate to adaptive immunity in the pathophysiology of psoriasis

Innate immature cells produce key cytokines (TNF-α, interferon- α, interferon-γ, interleukin-1β and interleukin 6) that activate myloid dendritic cells. Activated dendritic cells present antigens and secrete mediators such as interleukin-12 and interleukin-23, leading to the differentiation of type 17 and type 1 helper T cells (Th17 and Th1). T cells, in turn, secrete mediators (e.g. interleukin-17A, interleukin-17F, and interleukin-22) that activate keratinocytes and induce the production of antimicrobial peptides (e.g.LL-37 cathelicidin and β-defensins), proinflammatory cytokines (TNF-α, interleukin-1β, and interleukin 6), chemokines (CXCL8 through CXCL11 and CCL20) and S100 proteins. These soluble mediators feed back into the proinflammatory disease cycle and shape the inflammatory infiltrate.

It seems possessing the gene encoding the IL23 receptor (IL23R) confers strong protection against Crohn Disease [97] Chan et al showed other molecules cross talk between IL23 activated monocytes and the epidermal response including TNF-α and members of the IL19 mainly (IL19, IL20, IL24). IL23 induced epidermal response was depended on the presence of TNF-α as well as the IL20R receptor – which is shared by IL19 family members. There is observed reciprocal exchange of signals between epidermal keratinocytes and immunocytes.

An effort has been ongoing to search for that elusive high-affinity foreign antigen possibly derived from an infectious agent to drive the distinct cell clones in the clonal adaptive immune response. However, to date, no clonal T-cell expansion has been consistently indentified. Alternatively, investigators began to look at the innate immune system as the

one responsible for contributing to an inappropriate local tissue inflammatory reaction in psoriasis. It has been noted that IL-23 has been implicated in local mucosal immunopathology by means of innate immune mechanisms. [98] Noting that dendritic cells serve as the bridge between the innate and the adaptive immune system, it may well be it is not an antigenic stimulus that sparks the process, but a genetically programmed hyperactivity of these cells through their altered mechanism of immunologic synapse.

As a final thought in this section, vitamin D and its analogs have been well established as therapeutic agents in the treatment of psoriasis. The mechanism of action by which these agents improve psoriasis is via the vitamin D receptor (VDR), which mediates its effects on the proliferation and differentiation of epidermal keratinocytes,[99] [100] and on the immunological features of psoriasis, including shifting the T_H 1 cytokine profile of plaques towards a T_H 2 cytokine profile. [101]

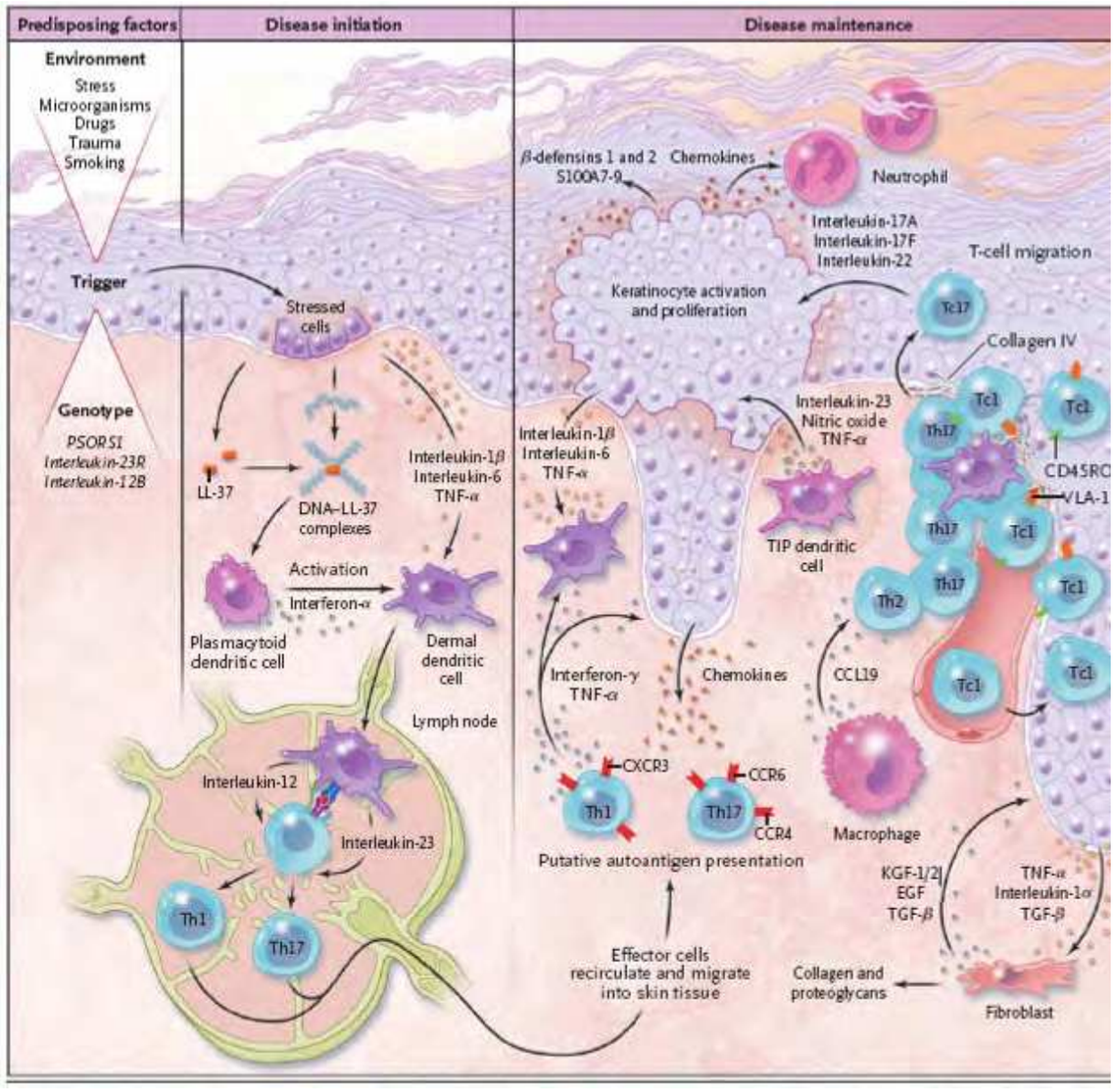


Fig. 9. Overview of the immunopathophysiology of Psoriasis

Vitamin D, through its action by interaction with the VDR offers a beneficial effect on reducing the psoriatic plaque. Keratinocyte differentiation is evident through observed increased levels of transglutaminase I and involucrin and enhanced cornified envelope formation of suprabasal cells [102] [103] , and down regulation of epidermal growth factor, keratin & other markers. The immunomodulatory activity of VDR includes a decrease in the expression or protein levels of IL-2, IL-6, IL-8, IFNγ and GM-CSF. These cytokines play a role in cutaneous inflammation and proliferation of T-lymphocytes and keratinocytes. The expression of IL-12 and GMCSF is negatively regulated through VDR by ligand-dependent inhibition of NF-AT-AP1 composite element activity. [104] [105] 1α,25-dihydroxyvitamin D3 and calcipotriol have also been shown to increase the expression of the receptor for the anti-inflammatory cytokine IL-10 in cultured keratinocytes. [106] [107]

The overall scheme illustrating the various players in the process that leads to the development of psoriasis is illustrated in Figure 2.

7. Comorbidities & other medical considerations

The basis for these observations began from noting psoriasis is characterized by increased T-cell activation leading to production of various cytokines leading to inflammation in the skin as well as other organ targets. 28 These next sections will look at recent data exploring the possibility of a link between psoriasis and cardiovascular disease, chronic obstructive pulmonary disease, metabolic syndrome and obesity, diabetes, pregnancy, celiac disease, and malignancies.

7.1 Cardiovascular disease

Psoriasis may be a risk factor for development of coronary artery calcification (CAC) according to a small study in which 32 patients with psoriasis and 32 matched controls were compared to assess their degree of CAC using non-contrast-enhanced, 16-row, spiral computed tomography. Patients and controls were matched for age, sex, race, cardiovascular risk factors with the exception of family history of cardiovascular diseases. CAC scores were determined for these various individuals and the scores were correlated with the likelihood of coronary artery disease (CAD). Nearly 72% of control patients were found to be free of evidence of CAC, as opposed to only 40.6% of psoriasis patients. In the category where stenosis was likely to be found (those with a CAC score 101-400), 9.4% of control subjects were found to have CAD in comparison with 18.8% in the psoriasis group. For those subjects with a CAC score above 400, no patient in the control group was found to have CAD; whereas 6.3% of the psoriasis group showed nearly certain evidence of CAD. [108] In one larger study investigators from the United Kingdom employed the General Practice Research Database (UKGPRD) to determine whether severe psoriasis is associated with an increases risk of cardiovascular mortality. They identified 3603 patients with severe psoriasis, and compared that to 14,330 who had no history of psoriasis. Severe psoriasis was defined as anyone given the diagnosis of severe psoriasis, and systemic therapy consistent with severe psoriasis. The unadjusted risk of mortality measures incidence per 1,000 person-years, due to cardiovascular disease, and was significantly increased in patients with severe psoriasis (8.75), compared with unexposed patients (6.19). Even as severe psoriasis was shown to be an independent risk factor for death due to cardiovascular disease, after adjusting for traditional cardiovascular risk factors (age, sex, hyperlipidemia, hypertension,

smoking, diabetes), the relative risk (RR) of cardiovascular death associated with severe psoriasis was highest in younger individuals with a RR of cardiovascular death of 2.69 for a 40-year-old, as opposed to 1.92 for a 60-year old. [109]

Using the UKGPRD, Gelfand *et al* embarked in a more ambitious prospective, population-based cohort study. Patients with psoriasis (aged 20 to 90 years) were compared with a matched sample of persons without psoriasis from 1987 to 2002. There were 555,995 controls, 127,139 patients with mild psoriasis, and 3837 patients with severe psoriasis (defined like in the previous study). The rates of myocardial infarction (MI) were compared between controls and psoriasis patients after a mean follow-up time of 4-5 years. Out of the group of patients with mild disease the adjusted relative risk for MI was 1.54, while the rate in the group having severe psoriatic disease was 7.08. Separating the groups according to age showed similar results as the earlier study. The younger individuals displayed a greater risk for MI than older patients, and severity of disease was again proportionally more likely to confer a greater risk in the younger age group. Additional analysis suggested men and women with severe psoriasis died 3.5 and 4.4 years younger respectively than patients without psoriasis. The results persisted after adjustment for risk factors associated with mortality. [110] Further evaluation of this data in a recent publication concluded severe psoriasis confers an additional 6.2% absolute risk of 10-year rate of major adverse cardiac events compared to the general population. This has important therapeutic implications for cardiovascular risk stratification and prevention in patients with severe psoriasis. [111]

Very similar results were obtained in a study of two US health care databases analyzed adult patients at least 17 years old in 2001. The population examined totaled around 17 million. Cardiovascular disease (CVD) or CVD risk factors generally increased with disease severity. Severe disease was defined as disease requiring at least one systemic drug. In both databases, higher disease severity raised the risk for coronary heart failure, diabetes mellitus (type 2), hypertension, and ischemic heart disease. [112] An observational study analyzed computerized records of all outpatients who were diagnosed with psoriasis between January 1, 1985 and December 31, 2005 at the Miami VA Medical Center. A total of 3,236 patients with psoriasis and 2,500 controls were evaluated. An association was observed between psoriasis and coronary artery, cerebrovascular, and peripheral vascular diseases.[113]

Osteopontin is a phosphoprotein secreted by osteoblasts, lymphocytes, macrophages, epithelial cells, and smooth muscle cells. It is a byproduct of inflammation, and has been known to be elevated in patients with atherosclerotic heart disease. Chen *et al* have noted increased levels of *osteopontin* in patients with psoriasis, and have suggested it be a cardiovascular risk factor for patients suffering with psoriasis, further validating the notion inflammatory factors may coexist in both heart disease and psoriasis. [114]

Anti-TNF therapy may reduce risk for MI in patients with psoriasis. A retrospective cohort group study at Kaiser Permanente in Southern California looked at 30,467 patients from January 2004 to December 2008 The average age was 50.2 years, with 48.4% being males. Severe psoriasis was defined as anyone getting systemic therapy including phototherapy. There were 5,392 (18%) patients in this group. The TNF-α inhibitor cohort had 2,064 (7%) patients. The overall MI rate was 0.42 per 100 patient years for all patients, while the cohort that had mild psoriasis had an MI rate of 0.43 per 100 patient year, and the severe psoriasis group had a rate of 0.44 per 100 patient years. Patients treated with a TNFα antagonist showed a rate of 0.34 per 100 patient years. This data suggest that effective therapy with a

TNF-α antagonist should reverse the cardiovascular risk profile for patients that respond to this therapy. Further research is needed before this claim can be verified. [115]

7.2 Metabolic syndrome & obesity

Metabolic syndrome is a cluster of risk factors that often accompany obesity, and is associated with increased risk for atherosclerotic cardiovascular disease and type 2 diabetes. The 5 components of metabolic syndrome, as defined by the United States National Cholesterol Education Program, are abdominal obesity (measured by waist circumference), elevated fasting glucose (suggestive of insulin resistance), hypertension, hypertriglyceridemia and, reduced high-density lipoprotein cholesterol (HDL-C). Persons meeting any 3 or more of these 5 criteria are now considered to have metabolic syndrome. The metabolic syndrome is a cluster of risk factors that often accompany obesity and are associated with increased risk for cardiovascular disease and type 2 diabetes. Certain adjustments to waist circumference measurement should be made for persons of Asian origin (cut point ≥ 90 cm in men and ≥ 80 cm in women). The prevalence of metabolic syndrome in the US is estimated to be 22.8% among men and 22.6% among women. It is highest among those of Mexican-American heritage and lowest in blacks. [116] [117] [118]

It has been suggested that there may be a relationship between the risk of psoriasis, and obesity. Both conditions result in a state of chronic systemic inflammation that can have deleterious effects on cardiovascular health, glucose, and lipid metabolism. Obesity is associated with a state of chronic low-level inflammation and the presence of inflammatory cytokines, particularly tumor necrosis factor alpha (TNF-α), which are presumed to derive from macrophages into adipose tissue or activated adipocytes themselves. [119] **[120] [121] [122] [123]**

Adipocytes (fat cells) store lipids and regulate metabolic homeostasis under normal conditions, while macrophages play a key role in the inflammatory response.

However, each has the ability to perform both functions if necessary. Both types of cells share certain common features, including production of inflammatory cytokines and fatty acid binding proteins. In obese persons, infiltration of macrophages into adipose tissue and release of inflammatory cytokines by adipocytes results in adipocytes becoming inflamed. Several of the cytokines released by adipocytes affect the immune stress response, and many more are key to inflammation (TNF-α, interleukin-6).[124] [125] [126]

In a recent survey conducted by the National Psoriasis Foundation, many psoriasis and psoriatic arthritis patients surveyed reported having at least one other critical health condition. Of those surveyed, almost 70% were overweight or obese; 28% had another chronic inflammatory disease such as lupus, Crohn's disease, or multiple sclerosis; while 24% of patients had hypercholesterolemia. Survey responses were obtained between 2004 and 2009 from telephone and internet surveys. Survey respondents were screened so that 75% had moderate to severe psoriasis, based on expected body surface area (BSA) coverage of 3% or greater without medication, while the remaining 25% had mild disease, or BSA coverage of less than 3%. Among respondents, 62% had psoriasis alone, while 38% also had psoriatic arthritis. [127]

Using the WHO definition of metabolic syndrome, a retrospective study compared records of 581 adults hospitalized with chronic moderate to severe plaque psoriasis with those of

1,044 hospitalized controls without psoriasis. The patients with psoriasis had chronic plaque disease requiring hospitalization because of the severity of their disease or treatment resistance. The median duration of psoriasis was 13 years for men and 16 years for women. Metabolic syndrome was found in 4.3% of the chronic plaque psoriasis patients and only 1.1% in the control group. These psoriasis patients were at significantly increased risk for type 2 diabetes, hypertension, dyslipidemia, and coronary heart disease, and were also more likely to consume alcohol and to be smokers than controls. [128]

Another case-controlled study compared 338 adult patients with psoriasis and psoriatic arthritis and 334 patients with non-psoriatic skin diseases to see if metabolic syndrome was more common among the former. In this study, the mean age of patients was 62.1 years in the control group and 63.8 years in the psoriasis group, and more persons in the psoriatic diseases group were smokers. Fifty five percent of psoriasis patients had BSA ≥ 10%, 43% had PASI scores ≥ 10. [129] In a retrospective case-control study, information from the database of a large managed care organization, with approximately 3.8 million members, was used to assess the potential association between metabolic syndrome and psoriasis. In total, nearly 17,000 patients with psoriasis and 49,000 controls were included; about half were women. The proportion of patients with conditions associated with metabolic syndrome, such as diabetes mellitus, hypertension, and obesity, were increased in those with psoriasis versus controls. Triglyceride and total cholesterol levels were also higher in the psoriasis group by a small but significant amount. [130]

7.3 Diabetes

The association of psoriasis with obesity and diabetes is implicitly evident with the data presented under metabolic syndrome. In a population-based observational study using the UKGPRD, the electronic records of about 73,000 patients were examined between 1994 and 2005. The group was matched between those with a first-time diagnosis of psoriasis and those without. Analysis showed that, as compared to those without psoriasis, the odds ratio (OR) of developing diabetes mellitus in those with psoriasis was 1.31. This odds ratio was corrected for smoking status, body mass index (BMI), hyperlipidemia, infections, and systemic steroid use. Among overweight patients (BMI=25), the OR of developing diabetes mellitus, as compared to normal weight patients, was 7.04 among overweight patients without psoriasis, but this OR was elevated to 8.27 among overweight patients with psoriasis. The risk of developing diabetes mellitus in the psoriasis cohort appeared independent of BMI. Specifically, the risk for developing diabetes mellitus in psoriatic patients of normal weight, or BMI less than 25, increased twofold, 2.02, compared with normal weight patients without psoriasis. [131]

To evaluate further the potential relationship between obesity and psoriasis, Setty and colleagues conducted a prospective, 16-year longitudinal study that evaluated the relationship between adiposity and incidence of psoriasis in a prospective cohort of nearly 117,000 female registered nurses who were between the ages of 25 and 42 years and who had no previously diagnosed psoriasis. The study investigators measured body mass index (BMI), weight change, waist circumference, hip circumference, waist-hip ratio, and incident psoriasis. Data were collected in 78,626 women and in the study time period, 892 newly diagnosed cases of psoriasis were identified. Using a BMI of 21.0 to 22.9 as the

reference, the relative risk of psoriasis increased significantly as the BMI increased in all three evaluations: updated, baseline, and after18 years. In the baseline evaluation, the relative risk for the 30.0-34.9 BMI range was 1.73, rising to 2.23 when the BMI was greater than or equal to 35. For the updated evaluation, which was updated every 2 years during follow-up, the relative risk was 1.48 in the 30-34.9 BMI range, and 2.69 when the BMI was over 35. Additionally, a BMI value under 21 was associated with a lower psoriasis risk. Taken together, these data show that multiple measures of adiposity, such as BMI, weight gain since the age of 18, and waist and hip circumference, are substantial risk factors for the development of psoriasis. [132]

Using the same study that began in 1989, Qureshi and colleagues published data on the risk of diabetes and hypertension in female patients with psoriasis. Out of 84,039 women who responded to a questionnaire in 2005 regarding psoriasis, 5,978 women were excluded due to reporting diabetes or hypertension at baseline. Out of the remaining 78,061 women, 1,813 reported a lifetime history of physician-diagnosed psoriasis. During the 14-year follow up from 1991 to 2005, 1500 incident cases of diabetes occurred in the group without psoriasis and 60 incident cases of diabetes occurred in the group with psoriasis. Of those that did not have psoriasis, there were 15,338 incident cases of hypertension and 386 incident cases of hypertension in the group that reported psoriasis (excluding any individuals with concomitant diabetes and hypertension). Mean BMI, alcohol intake, and proportions of current and past smokers were higher in the psoriasis group. There was no difference in mean age between the groups with and without psoriasis. Concomitant psoriasis therapies were unknown. [133]

7.4 Chronic Obstructive Pulmonary Disease (COPD)

More recently Chiang & Lin looked at the National Health Insurance database in Taiwan from 2004 to 2006. The risk of COPD was compared between patients with psoriasis and a matched reference cohort. Their study included 2096 patients with psoriasis and 8384 randomly selected subjects. After adjusting for sociodemographic characteristics and selected co-morbid medical disorders, results showed a hazards ratio (HR) of COPD for mild psoriasis (defined as those just getting topical therapy) to be 2.22. Patients in the comparison cohort with severe psoriasis (defined as those under phototherapy or systemic medication) had an HR of COPD of 2.81. Analysis stratified by patient age and gender showed an adjusted HR for COPD occurring during the 18-month follow-up period to be 2.19 times higher for patients with psoriasis who were > 50 years old than for the same age group of the comparison cohort. There was no significant difference in patients ≤ 50 years old. In male subjects, the adjusted HR of COPD during the follow-up period was 2.38 times greater for those with psoriasis than those without; however, there was no significant difference in the female group. This study places a distinct association among male patients with severe psoriasis, especially those over 50 years of age and psoriasis.[134]

7.5 Venous thromboembolism

Using the multivariate Poisson regression model controlling for age, gender, comorbidity, concomitant medication, socio-economic data and calendar year, Ahlehoff *et al* looked at data from a Danish nationwide cohort derived from records of hospitalization, drugs

dispensing from pharmacies, socio-economic data, and listed causes of death. The intent was to look at the risk of venous thromboembolism (VTE) in patients with psoriasis. A total of 35,138 patients with mild psoriasis and 3,526 patients with severe psoriasis were identified, and compared with 4,126,075 controls. The rate ratio (RR) for VTE was elevated in all patients with psoriasis, with RR 1.35 for mild psoriasis, and RR 2.06 for more severe disease. Excluding patients with malignancies and undergoing surgery did not alter results. There was a highest risk noted in young patients with severe psoriasis.[135]

7.6 Pregnancy

Pregnant women with psoriasis (n = 47) and non-pregnant controls (n = 27) were assessed 5 times over 1 year at approximately 10, 20, and 30 weeks of pregnancy and 6 and more than 24 weeks postpartum. A change of more than 3% body surface area defined "Improvement" and "Worsening"; no change was defined as a change in body surface area between 3% and -3%. Most pregnant women with psoriasis experienced improvement in psoriasis or no change during their pregnancies. Psoriasis worsened in fewer than one-fourth of the patients. Conversely, nearly two-thirds of the patients experienced worsening of their psoriasis postpartum. [136] Retrospective examination of psoriasis data from 358 women with psoriasis and 131,424 without psoriasis indicates that psoriasis may be associated with poor pregnancy outcomes, including: spontaneous abortion risk ratio (RR) 3.90; preterm birth RR 2.92; severe pre-eclampsia and eclampsia RR 4.92; *placenta previa* with/without hemorrhage RR 3.49; and ectopic pregnancy RR 4.56. [137] Many of the treatments to be discussed later need to be avoided in the pregnancy state.

7.7 Celiac disease

The association between psoriasis and celiac disease has already been mentioned. Patients with psoriasis often have increased serum levels of IgA antibodies to gliadin. Out of 302 patients with psoriasis, 16% (18 females and 31 males) showed serum IgA

Anti-Gliadin A (AGA) levels above the 90th percentile value (51 u/ml) of the reference group. Palmoplantar pustulosis was found more often than other types of psoriasis. Some patients had signs of gluten sensitive enteropathy. It is noteworthy that 10% of patients with celiac disease fail to show AGA. [138] Out of 33 AGA-positive patients with psoriasis patients, 15 had an increased number of lymphocytes in the duodenal epithelium, and two had IgA antibodies to endomysium (EmA). Thirty of the 33 patients with AGA completed a gluten-free diet for a trial period, after which they showed a highly significant decrease in mean PASI. Resumption of a regular diet resulted in a return of pre-study psoriasis. [139]

7.8 Malignancies

Using the UKGPRD populations of 153,197 from 1988 ton 2002, patients with psoriasis (including 3994 with severe psoriasis) and 765,950 matched controls were identified for a retrospective cohort analysis. Psoriasis patients were classified as severe if they received a systemic treatment. It is important to note that the disease severity classification was based on the treatment the patient had received. The potential causal relationship between therapy and risk of malignancy was not addressed in this study. Highest risk was noted on the occurrence of T-cell lymphoma among the severe psoriasis population. [140]

Adjusted Relative Risk (RR, 95% CI)*	Mild Psoriasis	Severe Psoriasis
All lymphoma	1.34 (1.16, 1.54)†	1.59 (0.88, 2.89)‡
Non-Hodgkin's lymphoma £	1.15 (0.97, 1.37)‡	0.73 (0.28, 1.96)§
Hodgkin's lymphoma	1.42 (1.00, 2.02)**	3.18 (1.01, 9.97)**
T-cell lymphoma	4.10 (2.70, 6.23)†	10.75 (3.89, 29.76)†
*RR = relative risk(confidence interval), adjusted for gender and age † P <0.001 ‡ P <0.1 § P = 0.5 ** P = 0.05 £ Excludes cutaneous T-cell lymphoma		
(Gelfand JM, Shin DB, Neimann AL, Wang X, Margolis DJ, Troxel AB. The risk of lymphoma in patients with psoriasis. *J Invest Dermatol*. 2006;126:2194-2201.)		

Table 3. Risk of Lymphoma in Psoriasis (UK General Practice Research Database) 28

A study in Sweden examined records of patients with a hospital discharge diagnosis of psoriasis between the years of 1965 and 1983, and identified 9,773 patients who were alive and free of cancer one year after admission. Relative rates of cancer were compared to the Swedish national population by computing the standardized incidence ratios (SIR). The table gives the SIR for different cancer types. The most commonly seen cancers were prostate in men (77 cases) and breast in women (78 cases). Other common cancers were lung (65 cases in men, 25 in women), colon (26 cases each in men and women), and squamous cell cancer of the skin (35 cases in men,10 in women). An increased risk of squamous cell cancer was seen in all anatomic regions except the head and neck. However, no increased risk of melanoma was seen with psoriasis. [141]

SIR (95% CI)	Male	Female	Both Genders
Oral/Pharyngeal	2.60 (1.68-3.84)	3.37 (1.68-6.04)	2.80 1.96-3.87)
Esophagus	3.00 (1.59-5.13)	3.03 (082-7.76)	3.01-1.75-4.81)
Liver	2.52 (1.49-3.98)	1.36 (0.68-2.44)	1.91 (1.28-2.74)
Pancreas	1.34 (0.73-2.24)	1.82 (0.99-3.05)	1.56 (1.02-2.23)
Lung	1.91 (1.48-2.44)	3.00 (1.94-4.43)	2.13 (1.71-2.61)
Skin, Squamous Cell Carcinoma	2.75 (1.92-3.83)	1.92 (1.02-3.28)	2.46 (1.82-3.27
Genital organs	2.69 (1.16-5.30)	2.47 (0.90-5.37)	
Kidney, pelvis	1.10 (0.58-1.88)	2.45 (1.37-4.04)	1.56 (1.04-2.25)
Mycosis fungoides	26.7 (8.60-62.3)	0.07 (0.51.3)	19.3 (6.22-45.1)
Non-lymphocytic leukemia	1.74 (0.64-3.79)	2.18 (0.70-5.09)	1.92 (0.96-3.43)
* Incidence ratio of select neoplasms among patients hospitalized for psoriasis			
Boffetta P, Gridley G, Lindelof B. Cancer risk in a population-based cohort of patients hospitalized for psoriasis in Sweden. *J Invest Dermatol.* 2001;117:1531-1537.			

Table 4. Prevalence of Malignancies in Psoriasis * (Swedish Hospital Study) 28

A cohort US study assessing incidence of cancer in 1,105 patients with severe psoriasis and 16,519 patients with less severe psoriasis looked at patients in the government public assistance program of three states from July 1992 to March 1996. One state was located in the mid-Atlantic region, one in the midwest, and one in the southern region of the US The states were not identified. The incidence of cancer in the psoriasis population was compared with the general population (N=259,808). Margolis *et al* designed a 4-year retrospective cohort study using Medicaid data from three large states to compare the risk of malignancy among adult patients ≥ 20 years with severe psoriasis treated with ≥ 1 systemic agents and less severe psoriasis not treated with a systemic agent. Comparison groups included patients with hypertension, patients with severe eczema, and organ transplant recipients. The hypertension group was selected as the reference group because the cancer risk among hypertensive persons is not expected to be substantially different from the risk in the general population.

Patients with severe psoriasis were more likely to develop a malignancy than those patients in the hypertension, severe eczema, and less severe psoriasis groups.

Patients with less severe psoriasis may have had a slightly increased risk of developing cancer compared with the hypertension group. A limitation of this study is that it did not differentiate between potential causes for increased risk of cancer: psoriasis severity and systemic agent use. [142]

Relative Rate Ratio (RR, 95% CI)*	Less Severe Psoriasis	Severe Psoriasis †
All malignancies	1.13 (1.03-1.25)	1.78 (1.32-2.40)
Lymphoproliferative malignancies	2.11 (1.63-2.74)	7.95 (4.94-12.79)
Skin malignancies (non-melanoma & unknown behavior	2.35 (1.96-2.82)	4.15 (2.52-6.84)
Malignancies(excluding non-melanoma skin and lymphoproliferative malignancies	1.00 (0.90-1.12)	1.46 (1.04-2-05)
* Poisson regression used to estimate relative rate ratio compared with hypertensive population adjusted for age, patioent's state of origin, and sex. † Psoriasis patients were classified as severe if they received treatment with systemic medications.		
Margolis D, et al. *Arch Dermatol*. 2001;137:778-783.		

Table 5. Prevalence of Malignancies in Psoriasis (US Study)

7.9 Management of psoriasis & psoriatic arthritis

Studies looking at cognitive behavior therapy as an adjunct to pharmaceutical therapies in patients with psoriasis showed clinical improvement in comparison to patients receiving pharmacological therapy alone. [143] High levels of worry and stress have been found to aggravate disease activity, and aggravate the therapeutic benefit of Psoralen and UVA therapy (PUVA). [144] Attempts to look at diet including diets rich in zinc, [145] and turkey meat, [146] diets low in tryptophan, [147] protein, [148] or calories [149] seem to have little impact. As mentioned before, in patients with both celiac disease and psoriasis, diets low in gluten have been shown to be useful in improving both conditions. 28

It is well documented sunlight exposure (heliotherapy), and spa treatments such as those in the Israeli Dead Sea can be beneficial. [150]

Traditionally, pharmacological therapy has been divided into topical therapy, systemic therapy and photo-pharmacological therapy (PUVA). Some include all forms of phototherapy in systemic therapy. Before steroids were introduced, topical therapy was limited to tar, anthralin and keratolytics like urea and salicylic acid. The impossibility to standardize biological activity on tar products, and arrive at a consensus on measuring disease severity to gauge therapeutic success has hindered the ability to define and compare various reported efficacies of these topical regimens.

7.10 Tar with & without UV therapy

Tar had been used as topical monotherapy for a century before it was combined with Ultraviolet B (UV-B at 290-320 nm) in the Goeckerman regimen. [151] Crude coal tar (2.5-5%) was applied daily in combination with a tar bath and UV therapy, usually as an inpatient facility. It became clear UVB was more valuable than UVA. [152] In addition, tar could sensitize the skin to UVA, but not UVB. It is believed UVB erythema thresholds prevent UVA exposure sufficient to cause photosensitization in the Goeckerman regimen. [153] The risk from therapeutic tar is small. [154] [155] It may be wise to avoid prolonged application to the anogenital areas including the scrotum, and avoid prolonged UV exposure. [156] [157] [158] [159]

7.11 Anthralin (dithranol)

Chrysarobin, from the bark of a tree, was found to be useful in the treatment of psoriasis. Dithranol, a synthetic derivative, was found to be unstable, but salicylic acid was found to stabilize it and lead to the development of the Ingram regimen. [160] After a tar bath, followed by UVB, the lesions were covered with dithranol paste in increasing concentrations seeking a maximum response while avoiding irritation. The regimen became popular in Europe. It was later found use of dithranol in Lassar's paste was equally effective. Short contact dithranol therapy – twice daily and in high concentration regimes, was also effective. [161] Newer formulations have been developed to limit staining and reduce irritation. In some parts of the world, anthralin is available as a combination preparation with potent topical steroids, and effective results have been seen. [162]

7.12 Topical corticosteroids

Held by many as the topical treatment of choice, several preparations are widely available worldwide. The more potent forms of topical corticosteroids, are needed to treat hyperkeratotic plaques, and difficult to treat areas like the scalp, hands and feet. Besides their direct effect in limiting psoriasis, these agents are helpful in reducing symptoms like pruritus, and limiting irritation caused by other therapies. Better results are often obtained using occlusive dressings; a recent study found even better effectiveness when occluded with a hydrocolloid dressing. [163] Cutaneous side effects include telangiestasias, atrophy and striae. [164] Besides cutaneous adverse events adrenal suppression leading to lowering plasma cortisol levels can be observed with the most-potent preparations. [165] As little as 7 g/day of 0.05% clobetasol propionate or 0.05% betamethasone dipropionate was sufficient to suppress morning plasma cortisol levels in 20% of patients. [166] Tolerance or tachyphylaxis is

not uncommon. To avoid this, as well as other adverse side effects, sequential therapy incorporating other topical agents, and pulse therapy rotating the various agents, have been implemented limiting total contact with skin, and any significant absorption. [167] [168] [169]

7.13 Intralesional corticosteroids

Resistant and thick plaques in awkward anatomical areas, like the knuckles, where it is difficult to keep topical preparations during daily living activities, often respond to intralesional injections with triamcinolone acetonide with remarkable success.

7.14 Vitamin D analogs

Naturally occurring and synthetic vitamin D analogues have been found to be effective in the topical treatment of psoriasis. Vitamin D_3 and its active metabolite, 1,25 dihydroxyvitamin D_3, (calcitriol), as well as the three synthetic analogues – calcipotriol (known in the US as calcipotriene), 1-24-dihydroxyvitamin D_3 (tacalcitol), and 1,25-dihydroxyvitamin D_3 (maxacalcitol). Calcipotriol ointment is the most widely prescribed vitamin D analog. The mechanism by which these molecules affect their therapeutic benefit has already been described in a previous section. Current concern on their use includes irritation, and the potential for hypercalcemia, which has not been observed with the use or recommended maximum topical dosing of up to 100 g/week. [170] Ointment preparations appear to be more effective than the others available. A combination stable formulation using calcipotriol 50 µg/g and betamethasone diproprionate 0.5%mg/g, applied once daily shows better results than either product alone. [171] Calcitriol ointment 3 µg/g has shown long term effectiveness in the treatment of chronic large plaque psoriasis. Comparison between this agent, calcipotriol and other topical agents used to treat psoriasis show unclear results except for the superiority of calcitriol in the treatment of face and flexural regions, and a lower relapse rate following withdrawal compared with topical steroids. [172] [173] Tacalcitol 4 µg/g ointment is effective in the treatment of chronic plaque psoriasis, but does not appear to show superiority to calcipotriol 50 µg/g. [174] Preliminary studies indicate maxacalcitol applied once daily may be more effective in short-term studies than calcipotriol 50 µg/g. [175]

It is important to note salient interesting interactive relations when considering use of vitamin D analogues. Use of calcipotriol 50 µg/g used in combination with methotrexate allows the use of lower doses of methotrexate. [176] Clinical and *in vitro* studies have been performed analyzing the compatibility of using clobetasol propionate spray or lotion together with calcitriol ointment 3 µg/g. Results suggest calcitriol remains stable in the presence of each of the other compounds. The sequence used was not relevant to their continued efficacy. [177] [178]

Calcipotriol ointment enhances the efficacy of PUVA and UVB therapy, Howeverr, UVA partly inactivates calcipotriol, while UVB serves to absorb calcipotriol. When used with phototherapy, these products should be applied after the UV therapy session. 28 Tacalcitols ointment when combined with PUVA is UVA sparing, [179] while calcitriol is UVB sparing when used in combination. [180]

When used in combination with topical steroids, vitamin D analogs offer the advantage of sustained efficacy while offering a desirable steroid sparing effect. [181] This has lead to a wide

range of pulsing and sequential therapy regimens with anecdotal reports attesting to their efficacy. Controlled corroborating studies are lacking.

7.15 Vitamin A analogs

Retinoids have been suspected to be a successful alternative to the treatment of psoriasis. With their direct effect on cellular proliferation and subsequent differentiation, it would be expected they would be the ideal preparation. Initial trials revealed efficacy, but significant irritation. [182] The development of the products that selectively used the retinoid acid receptor ushered in tazarotene, a synthetic retinoid, whose main metabolite binds the RARs β and γ. [183] Applied as its 0.05% or 0.1% gel once daily for three months, showed significant improvement over its gel vehicle in the treatment of chronic plaque psoriasis. [184] Irritation was its principal drawback, which was reduced when the 0.05% and 0.1% creams were introduced. [185] Reports using a topical steroid helped maintain a longer standing remission, while reducing some of the irritation. [186]

7.16 Topical calcineurin inhibitors

The two products in this category currently available are tacrolimus and pimecrolimus. Developed initially for the treatment of childhood atopic dermatitis, both preparations have been found effective for the management of psoriasis involving the face, neck, flexular areas, the genitals and mucosal surfaces. They have a safer profile than topical steroids, and do not produce skin atrophy where used. [187]

7.17 Phototherapy

7.17.1 UVB

The Goeckerman regimen, which used UVB was already described [188] Subsequent to the time this treatment was being offered, it was learned that broad band UVB at 290-320 nm (BBUVB) alone was effective in clearing psoriasis [189] [190] [191] [192] and even as effective as PUVA [193] While some studies have not shown an increased rate of skin cancer risk in UVB treated psoriasis patients [194] [195] [196], suspicion still exists that long term exposure may contribute to total risk. One study does suggest an added risk for genital tumors in men treated with BBUVB, [197] making it prudent to protect that area during treatment. More recently, a narrow-band source of UVB at 311nm, (NBUVB) has offered longer remissions, and suggested a lower incidence of burning. [198] [199] [200] Studies comparing a higher intensity (100W) NBUVB have suggested better results still. However, when compared to PUVA several studies provide conflicting results suggesting patient selection, level of disease activity, and need for larger population studies are needed before reliable results can be compared. [201] [202] [203] Data showing a lower risk for UV carcinogenesis is limited to one study, which failed to reveal significant association between NBUVB and squamous cell carcinoma, malignant melanoma and basal cell carcinoma. [204] One observation peculiar to NBUVB, which has not been observed in BBUVB, is the occurrence of painful blisters at the site of psoriatic lesions appearing in the middle of the treatment course. They are self limiting, but can be painful and require a brief interruption in the regimen. [205] Both NBUVB and BBUVB units are commercially available for home therapy.

In addition, end results can often be improved by supplementing phototherapy with topical dithranol, and oral retinoids, Heliotherapy, described previously, enjoys the therapeutic benefit of the full-range light spectrum of the sun. A retrospective study looked at 1488 psoriasis patients treated at a Dead Sea Clinic from 1983 to 1986. Patients were treated by sun exposure and bathing in the mineral-rich sea. Nearly three quarters improved by 90% or more. [206]

UVB can be used effectively for the treatment of guttate psoriasis, as well as those relatively rare forms of head and neck or "seborrheic" psoriasis. It is also helpful in patients who live in colder climates and experience seasonal exacerbation during winter months. UVB can also be used as adjunct therapy for a temporary period for patients who have responded to systemic therapy, but experience an unexpected setback in disease activity. Skin types should always be considered, especially if long-term care is a reasonable expectation, due to the potential for UV related carcinogenesis. This risk would be theoretically greater on individuals of Fitzpatrick skin types I-III.

7.18 Psoralen photochemotherapy (PUVA)

Success with the Goeckerman regimen, and use of psoralen photochemotherapy lead to thinking it might help psoriasis. [207] [208] By the early 1970's, there was ample evidence 8-methoxypsoralen (8-MOP) and UVA would treat psoriasis effectively, and thus lead to the treatment definition of photochemotherapy. [209] PUVA soon became its modified acronym. Other forms of psoralen like 5-methoxypsoralen (5-MOP) and trimethylpsoralen have been used with similar results as 8-MOP. [210] [211]

The treatment essentially involves the ingestion of one of several preparations of 8-MOP available at the recommended calculated dose. Bioavailability varies from various preparations, and from patient to patient. Intestinal absorption is affected by fat content. It is customary to use one preparation, take it on an empty stomach and insist on a constant time interval from ingestion to UVA exposure. Dose calculation based on weight is 0.6mg/kg given 2 hours before irradiation. Patients must wear appropriate eye protection for a period of 24 hours from the time the psoralen is ingested to prevent sun-induced cataracts. Treatment is given 2-4 times weekly. Initial UVA dose is based on skin type and is incrementally increased with each treatment by 0.5-1.5 J/cm^2 each time. [212] Once remission is achieved the frequency of treatment is gradually reduced and given every 1-4 weeks. Patient selection is important. Individuals must have physical stamina to stand for prolonged periods of time during the irradiation sessions. Previous exposure to arsenic, prior radiation therapy, pregnancy, and ingestion of medication that is photosensitizing are all contraindicated. Persons less than 18 years of age should not receive PUVA. Persons with any medical condition that can be exacerbated by UV exposure including patients with collagen vascular disease should be identified.

Clearance rates topping 90% have been reported, with substantial clearance being achieved with 15-25 treatments. [213] [214] [215] [216] [217] PUVA can be helpful in erythrodermic psoriasis, psoriasis involving palms and soles, pustular psoriasis, and psoriasis involving the nails. Results in these resistant forms of disease vary, and are not as successful. PUVA can be combined with dithronol, [218] methotrexate, [219] and calcipotriol.[220] Risk of cancer is increased further with concomitant methotrexate use. [221] Calcipotriol use reduces the required the UVA exposure, and as mentioned previously, should be used after irradiation to prevent its

inactivation. PUVA and UVB have been used effectively in patients who fail to response to PUVA or UVB alone. [222] Topical PUVA offers similar therapeutic advantage with fewer side effects. It is not generally available to the individual patient requiring in-patient administration, and thus too costly for practical use.

Early reports raised the concern that PUVA treated patients would experience an increased rate of developing tumors in patients with xeroderma pigmentosa. [223] PUVA appeared to have a promoter effect on patients previously exposed to X-irradiation, arsenic, and several cytotoxic drugs. [224] Subsequent studies have corroborated the same association with patients receiving PUVA. The risk is most profound on patients of fair skin. [225] [226] Stern et al reported an increase rate of squamous cell carcinoma among patients that received PUVA for a prolonged period of time. No association was found with malignant melanoma or basal cell carcinoma. [227] In a further follow-up study, the same group identified a risk for melanoma in association with long-term exposure to PUVA. [228] Subsequent Swedish study found a similar association with squamous cell carcinoma but no association with malignant melanoma or basal cell carcinoma. [229] Until more definitive studies define the proper course, current prudence suggests to avoid using PUVA on patients with family or past medical history of malignant melanoma, and to those that have already received 200 treatments. [230]

8. Systemic therapy

Systemic therapy is reversed for the more severe forms of psoriasis and the treatment of psoriatic arthritis. For the latter a Disease Modifying Anti Rheumatic Drug (DMARD) is generally used with the double aim of arresting inflammation, and halting disease progression. Some systemic agents can treat PsA while others do not.

8.1 Methotrexate (MTX)

An initial observation in 1951 demonstrated that aminopterin was beneficial in the treatment of psoriasis, and led to exploring use of its more stable analogue methotrexate, which can be administered orally, intramuscularly, subcutaneously and intravenously.[231] Its oral absorption may be impeded in psoriatic patients. [232] Twenty to 70% of methotrexate is bound to plasma albumin, [233] [234] [235] and excretion is largely by the kidney, but there is extensive entero-hepatic cycling. [236] [237] [238] Initially its mechanism was felt to be its anti-metabolite effect on keratinocyte proliferation through competitive inhibition of dihydrofolate reductase in DNA synthesis, [239] More recently, it has been learned that at low doses (0.1 to 0.3 mg/kg weekly), a dose too low to affect keratinocytes, methotrexate is 10-100 times more effective in inhibiting proliferation of lymphoid cells through its inhibition of 5-aminoimidazole-4-carboxamide ribonucleotide transformylase leading to accumulation of extracellular adenosine, which has anti-inflammatory activities including slowing chemotaxis of polymorphonuclear leukocytes. [240] [241] [242] These latter two mechanisms may have a greater effect on its ability to treat psoriasis. Addition of folic acid supplementation (1-5 mg/day) reduces the side effects of nausea, oral ulcers, and megaloblastic anemia.

Controlled trials attest to the effectiveness of methotrexate for the treatment of psoriasis. [243] [244] Initially 5-10 mg is given orally once a week to avoid early toxicity (the elderly can be started often with 2.5 mg). Doses can be increased by 2.5 mg/week to achieve a maximum of 25 mg/week. [245] Clinical response is generally noted within 2 weeks. Pustular psoriasis and

psoriatic erythroderma tend to respond to this regimen. Transient anorexia, nausea, and other upper gastrointestinal symptoms are the most common symptoms.

Before treatment, baseline renal, hepatic, and marrow function should be obtained. The presence of chronic hepatitis (B and C) should be ruled out. Due to methotrexate's direct effect on the immune system, latent tuberculosis, [246] and, where geographically appropriate, chronic fungal and other parasitic infection should be ruled out as well. [247]Since standard serum liver function tests cannot evaluate hepatic damage reliably, current guidelines suggest a liver biopsy be performed when a cumulative dose of 1.5 g is achieved, and repeated every 1.0-2.0 g thereafter. A liver biopsy has been the preferred method of monitoring the damaging effect of methotrexate, since serological liver function studies have been known to conceal evolving harm, and reveal significant hepatic scarring only too late in the course of therapy.[248] Hepatotoxicity is a well established effect of methotrexate. [249] [250] Renal impairment, previous intake of hepatotoxins, and alcohol use can increase this risk [251] In some parts of the world monitoring amino terminal type III procollagen peptide (PIIINP) assay every three months is being done in lieu of liver biopsy. In the US, the FDA has not approved the use of this assay yet. [252]

Myelosuppression is a serious issue with the use methotrexate. It can occur 7-10 days after an initial dose is given. It can also be seen in the setting of folate deficiency, as an initial response in the beginning of therapy, due to toxicity, or quite innocently when the patient receives sulfonamides or other drug (usually a sulfa based agent) interfering with dihydrofolate reductase activity. This is a potentially fatal reaction, and must be identified and treated with folinic acid given at a dose 20 mg. parenterally or orally, and repeated every 6 hours. [253]

There is no evidence that splitting the dose in three parts, and giving it every 12 hours, a practice that was common to synchronize the therapy to the keratinocyte cell cycle when it was believed the treatment was all about epidermal cell turnover, offers any advantage over single weekly dose, except when it comes to reducing nausea. Pharmacokinetic studies indicate the bioavailability of MTX after oral ingestion is highly variable and unreliable.[254] Subcutaneous administration offers the same advantage as intramuscular. Compared with the highly variable and unpredictable bioavailability following oral administration (25–80%), parenteral dosing achieves more consistent and complete absorption. [255] Intramuscular or subcutaneous administrations achieve equivalent pharmacokinetic profiles with a bioavailability of 87% of that following intravenous dosing.

Concern exists over the possible development of malignancies while on long-term therapy with methotrexate. Evidence supports an increase risk for developing cutaneous squamous cell carcinoma in those with cumulative doses in excess of 3 g over 4 years. Thus risk was independent of PUVA. Pneumonitis, oligospermia, and osteopathy can occur. The latter can be confused with psoriatic arthritis [256] Methotrexate is teratogenic, and an abortifacient in early pregnancy. [257] Conception is regarded safe 3 months after discontinuation of therapy. [258]

Methotrexate has been used in combination with UVB, PUVA, [259] and systemic retinoids.[260] Use with the latter must be done with caution due to greater risk of hepatitis. Methotrexate and cyclosporine helps patients with psoriatic arthritis [261], while combining methotrexate with colchicine has been used in generalized pustular psoriasis. [262]

8.2 Cyclosporine

Used principally as an immune-suppressant in organ-transplant recipients, cyclosporine is a cyclic undecapeptide derived from the fungus *Tolypocladium inflatum gams*. It was found to clear psoriasis in 1979. [263] Its mechanism of action is presumed to be related to its inhibitory effect on T-cell activation. [264] Because of it toxic effects, and its potential to cause malignancies, its use is generally limited to patients that have failed other systemic alternatives. Exclusion criteria for its use include renal dysfunction, uncontrolled hypertension, past or present malignancy, epilepsy, acute infections, other immunosuppressive therapy, concomitant therapy with neurotoxins, previous serious side effects from prior use, or known hypersensitivity. Candidates for using cyclosporine must be reliable to undergo proper frequent monitoring. As a highly lipophilic agent metabolized in the liver by means of the cytochrome P-450, there are many drugs that could interact with cyclosporine such as anticonvulsants, which can prevent therapeutic levels of cyclosporine. NSAIDs (non-steroidal anti-inflammatory drugs) may enhance nephrotoxicity. [265] The recommended initial daily oral regimen is 2.5 mg/kg divided in two doses. Improvement often starts in days, and failure to see any benefit in two weeks should warrant a dose escalation to a maximum of 5 mg/kg/day.[266] Sudden withdrawal may lead to relapse, but nothing like the flares seen with systemic steroid withdrawal.[267] [268] Ideally, this should be limited to 3-4 months.[269] [270] In the US, the FDA recommends cyclosporine should be used for less than one year. One study compared intermittent cyclosporine with continuous use for psoriasis, and found an intermittent regimen was probably safer. [271]

Dose-related hypertension and nephrotoxicity are the most serious side effects associated with cyclosporine use. Blood pressure can increase sharply weeks after beginning therapy. Glomerular filtration rate may decrease while plasma creatinine levels may rise. Serum uric acid may rise prior to elevation in creatinine or blood urea nitrogen. Other side effects include gum hyperplasia, hypertrichosis, elevated sebum production, mild anemia, and paraesthesias. [272] The mechanism by which cyclosporine reverses the clinical signs of psoriasis is by blocking transcription and synthesis of lymphokines such as interleukin-2 (IL-2) and interferon-y (IFN-y). [273] [274] This product inhibits the accessory cell function of Langerhans cells, [275] decreases the capacity of dendritic cells to enhance mitogenic stimulation of lymphocytes, and induces secretion of thymic hormone. Thus, cyclosporine could inhibit cytokine-mediated cellular activation that may contribute to the pathogenesis and progression of this disease. [276] [277]

Immunosuppression with long term use of cyclosporine may be associated with an increased risk for cutaneous malignancies, lymphomas. This is seen especially in patients with previous history of getting UV irradiation in any therapeutic regimen, or arsenic and methotrexate. 28 Females observed to develop cervical intraepithelial neoplasia, and males with HPV-associated penile carcinoma suggests the need for frequent cervical smears for females and examination for males especially when there is prior history of HPV infection. [278] [279]

8.3 Oral retinoids

Retinoids refer to a family of natural and synthetic derivatives of vitamin A. Their role in skin physiology has been long established enhancing epithelial differentiation. Deficiency

causes squamous metaplasia and cutaneous hyperkeratosis, while their presence in excess can lead to xerosis with cutaneous exfoliation, hair loss, bony abnormalities, liver toxicity, and abnormalities in serum lipids. Oral retinoids are also well known for their teratogenic effect. They have been found to have a protective effect in slowing down or preventing the progression and development of cutaneous neoplasms arising out of chronic sun exposure. [280] [281] [282] While isotretinoin is the most widely known retinoid, used principally in the treatment of nodular acne and other forms of severe acne, and its successful use in the treatment of psoriasis has been documented, [283] other retinoids have been found more effective in the management of psoriasis. Because serum lipids are often elevated and hepatotoxic effects can occur with their use, proper monitoring is recommended.

8.4 Etretinate

First reported in 1975 to be useful in the treatment of psoriasis, [284] it was found effective for the treatment of psoriasis vulgaris, pustular psoriasis, [285] and erythrodermic psoriasis. [286] Its use has been replaced by acitretin in most countries.

8.5 Acitretin

This retinoid is the main active metabolite of etretinate. It has decreased lipophilicity resulting from being a free acid as opposed to an ester as in the case of etretinate. Its half life is 50 hours compared to 80 days for etretinate, making it a more desirable drug. Several clinical trials confer on acitretin the same profile of efficacy as etretinate. [287] [288] [289] [290] However, acitretin has been found to convert to etretinate in an unpredictable number of patients, requiring female patients of child-bearing age who use to refrain from pregnancy for 2 years after discontinuation of the drug. Retinoids should not be used in children except for exceptional circumstances, nor in anyone with pre-existing hyperlipidemia or liver disease. In the US, general practice is not to use an oral retinoid for psoriasis on any female of child-bearing age. Though a very small percentage of patients on acitretin may acquire a toxic hepatitis (1.5%), histological sign of hepatic damage is not found. Oral dosing can begin at 10 mg daily and increment to an optimum dose of 50 mg/day. Lipids should be monitored, and patients cautioned about photosensitivity. [291] The combination of acitretin with PUVA appears superior to PUVA alone. [292] Similarly acitretin improves the efficacy of UVB. [293]

Acitretin may help reduce the risk of cutaneous neoplasia brought on by chronic phototherapy. For this reason, its use has been advocated on patients with other risk factors for skin cancer who have received extensive phototherapy. 28 [294]

8.6 Systemic corticosteroids

Despite the fact that the use of systemic corticosteroids has not been advocated for the treatment of psoriasis, the practice of intramuscular injections with triamcinolone acetonide, commonly used for reduction of itching, inflammation, arthralgias and related symptoms associated with psoriasis, eczema, and other dermatoses is recognized as an effective clinical practice by many clinicians. However, in the case of psoriasis, there is often a break through of symptoms with repeated treatments. Rebound can also result. This phenomenon occurs often when patients with psoriasis undergo surgery. Current practice among

anesthesiologists is to administer a stress dose of corticosteroid prior to surgery, leading to an observed marked improvement of the psoriasis while in the hospital and following the immediate post-operative period. A rebound is generally noted a few weeks afterwards prompting a visit to the dermatologist's office. In spite of it all, systemic corticosteroids can be helpful in cooling down the skin during the erythrodermic phase of disease, especially if the treatment is supplemented with another systemic agent that can assist in bringing a remission. Systemic corticosteroids also have a place in the treatment of the von Zumbush reaction, [295] and the hyperacute polyarthritis with potential for joint damage. Lability of disease with steroids is common, and often difficult to dispel. [296] Systemic corticosteroids have been helpful with concomitant use of methotrexate in the management of rebound or acute flares associated with the use of efalizumab. [297]

8.7 Other systemic agents used for the treatment of psoriasis

8.7.1 Hydroxyurea

Hydroxyurea is an antimetabolite used mainly for the treatment of chronic myeloid leukemia among other malignancies. It is converted to its active metabolite which blocks the conversion of ribonucleotides to deoxyribonucleotides by blocking the action of ribonucleoside diphosphate reductase, and thus inhibiting DNA synthesis in proliferating cells. [298]

It was first conceived to be used on psoriasis in 1969.[299] Oral regimens are generally up to 0.5 g three times daily for a minimum of 2 months before considering the treatment suboptimal. Principal side effects include bone marrow suppression, profound anemia, and thrombocytopenia. Macrocytosis and leucopenia are practically universal. It is teratogenic, making it essential to be avoided during pregnancy. However, it is less hepatotoxic than methotrexate with less gastrointestinal side effects, and also less effective with a satisfactory response rate of 45-80%. [300] [301] [302] It is generally used when other systemic agents have failed, especially methotrexate. Besides, it can be used in combination with methotrexate, [303] cyclosporine, [304] and acitretin. [305] A drug related cutaneous vasculitis has been reported. 28 [306] Leg ulcers can occur, and are often difficult to manage. [307]

8.8 6-Thioguanine

Closely related to 6-mercaptopurine, 6-thioguanine was shown to be effective in the treatment of psoriasis. [308] [309] Its mechanism of action, as an antimetabolite, appers to be depletion of T-cells in the skin. The studies show remarkable efficacy in patients that had failed other systemic therapies. Oral regimens ranged in dose from 20 mg twice weekly to 120 mg/day, and the duration averaged 15 months. [310] [311] In one study 14 out of 18 patients experienced greater than 90% improvement. Increased liver enzymes and veno-occlusive disease of the liver may be seen. [312]

8.9 Fumaric acid

German speaking countries in Europe enjoy the most experience with the use of this family of compounds for the treatment of psoriasis. The mechanism of action seems to suggest the ability of fumarates to inhibit nuclear binding of nuclear Kappa B and promoting the secretion of Th2 cytokines such as IL-10, found to be beneficial in treating psoriasis. [313] [314]

Preparations commercially available incorporate several salts. Fumaderm is one such preparation with a mixture of dimethylfumarate, and the calcium, magnesium and zinc salts of monoethylfumaric acid. These compounds are not yet approved for use in the US. After ingestion, dimethylfumarate is hydrolysed to monomethylfumarate – the main active metabolite. Clinical trials show efficacy. [315] [316] [317] Regimen includes starting at 30 mg/day orally building up over several weeks to a maximum dosage of 240 mg three times daily. Dyspepsia and diarrhea are common appearing in about two thirds of patients, and one third develop flushing. Lymphocyte counts fall in nearly all, and can drop to 50%. Though it is prudent to monitor renal and liver function, it is rarely impaired.

9. Biologics – The latest modality

The mechanisms by which biologic agents exert their therapeutic benefit have been reviewed in the immunopathophysiology section of this chapter, and illustrated in Figure 1. In the US as in Europe and most parts of the world, their use is relegated generally to the patients suffering with moderate to severe disease, with or without psoriatic arthritis.

The Food & Drug Administration (FDA) approved the use of efalizumab in November 2003, and the European Medicines Agency (EMEA) in September 2004. This was one of several biologics approved for the treatment of psoriasis on the basis of favorable findings obtained from well-designed clinical trials. [318] Ongoing monitoring of sustained efficacy, tolerability, and possible side effects lead to the discovery of 3 newly diagnosed cases of progressive multifocal leukoencephalopathy. [319] In 2009, efalizumab was voluntarily withdrawn from the market by Genentech, its manufacturer. This unexpected experience underscores the importance of vigilance and careful monitoring when treating a medical condition with any immunosuppressant – biologics being no exception.

Another issue that relates to the use of biologics is the emergence of loss of therapeutic response. This may occur as a temporary minor flare of disease activity in spite of continuing use. It may also appear as a nearly total loss of therapeutic activity. Though this can occur with any biologic currently being used to treat psoriasis, it has been shown to occur more often with the monoclonal antibodies. It has been postulated this is due to the development of neutralizing antibodies, as in the case of infliximab and adalimumab, which generally follows with a subsequent drop in therapeutic serum level of the biologic being used.[320] Concomitant use of methotrexate at low doses has been shown to diminish chances of developing neutralizing antibodies. [321] Anti-adalimumab antibodies in rheumatoid arthritis patients have been recently reported to be associated with interleukin-10 gene polymorphism. [322] IL 10 is a key cytokine in antibody formation, and its role has been implicated in other autoimmune diseases. Neutralizing antibodies have not been detected to etanercept to date. Loss of response to the TNFα antagonists may also occur independent of adequate serum levels and lack of detectable antibodies. One thing is clear, the mechanism of loss of response is not as simple as one is lead to belief by reviewing current literature. One observation held by canvassing opinion from multiple thought leaders is resistance to therapy tends to arise early in therapy, and rarely after a patient shows adequate response to an agent for several years (personal communication). Further studies, especially comparative studies are needed to clarify the pathogenesis of this phenomenon, and learn which treatment is most appropriate to any given patient.

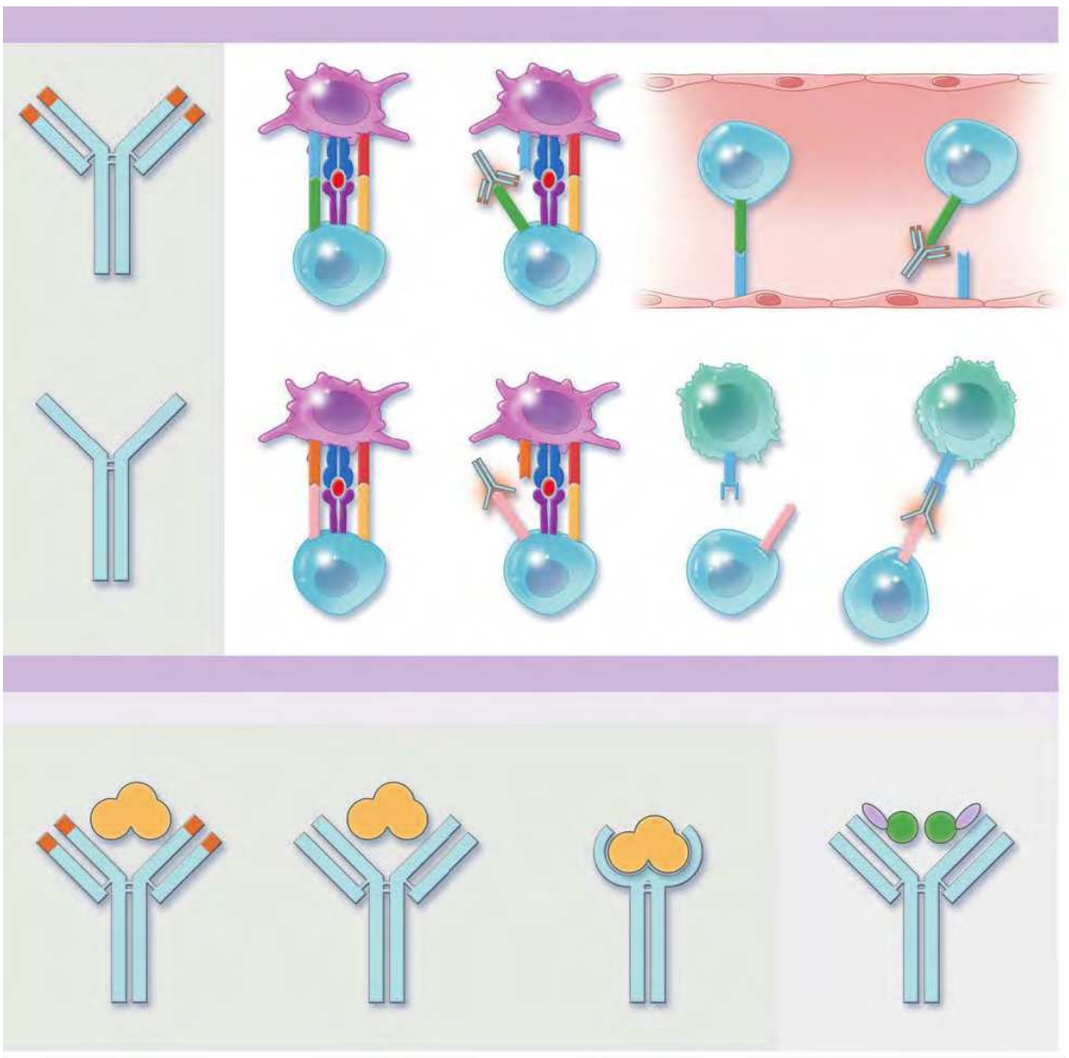


Fig. 10. Immunopathogenesis & Target Therapy (Legend)
New approaches to the treatment of psoriasis include targeted biologic therapies. Of those that been approved for marketing, the two major therapeutic classes are T-cell–targeted therapies (alefacept and efalizumab) and anticytokine therapies (anti–tumor necrosis factor [TNF] therapies): infliximab, adalimumab, etanercept, and a monoclonal antibody against interleukin-12 and interleukin-23 (ustekinumab). Efalizumab (which has been withdrawn from the market) is a chimeric monoclonal anti-CD11a antibody. It blocks the interaction of CD11a (lymphocyte-function–associated antigen -1 (LFA- 1) with intercellular adhesion molecule 1 (ICAM-1), leading to a disruption of the interaction between dendritic cells and T cells at tissue sites and in lymph nodes as well as blocking of immune cell binding to blood vessels. Alefacept is a human LFA-3 Fc fusion protein that blocks the interaction between CD2 on T cells and LFA-3 on antigen-presenting cells. It also induces antibody-dependent cytotoxicity in T cells bound to alefacept. At this point, anti-TNF strategies have three targeted therapies: a humanized chimeric anti–TNF-α monoclonal antibody (infliximab), a fully human monocolonal anti–TNF-α antibody (adalimumab), and a human p75 TNF-receptor Fc fusion protein (etanercept). Blocking of Il-12 and Il13 is achieved by means of antibodies targeting the common p40 chain of these cytokines. (CD=cluster designaton; FcR=Fc receptor)

Agent	Efficacy	Side effects
Sulfasalazine [323] [324] (anti-inflammatory)	57% of assessed patients in treated group showed marked improvement. Effective in psoriatic arthritis	25% patients get Headches, nausea, vomiting oligospermia, prutitis, anemia 1-2
Azathioprine [325] [326] (purine analog antimetabolite)	No conclusive studies	Bone marrow suppression
Mycophenolate mofetil (purine antimetbolite)[327] [328] [329]	Effective but with limited experience	GI and bone marrow
Cytokines IL-10 [330] [331] IL-4 [332]	 50% reduction in severity Short trials- 10 patients & 28 patients More than 68% improvement in 20 patients	 Mild anemia, decrease response in delayed-type hypersensitivity reaction
Zidovudine [333]	Improvement noted in AIDS-associated psoriasis - Of 19 evaluable patients, 90% had partial (58%) or complete (32%) improvement	Failed to improve associated arthritis, and long term relapses were common
Somatostatin [334] Liarozole (retinoic acid metabolism blockers) [335] [336]	Small series of patients, Similar to other systemic retinoids, but rapid clearance from blood once discontinued	Blood levels of somatostatin are inversely proportional to clinical response Teratogenicity, hyperlipidemias, and other muco-cutaneous symptoms
Photodynamic therapy (5-aminolevulinic acid followed by UVB irradiation) [337] [338]	Small series of patients – not all sites respond to treatment	Local pain at siote of therapy
Lasers Carbon dioxide and pulsed dye laser Excimer laser (308 nm UVB) [339] [340]	Insufficient data Effective especially when using high dose therapy with long remissions	 Potential for burning as with phototherapy

Oral calcineurin antagonists Oral tacrolimus [341] [342] Oral Pimecrolimus [343]	Oral tacrolimus can improve severe psoriasis in short term (10 weeks) Oral Pimecrolimus showed similar results	Paraesthesias, headache, elevation in serum creatinine, and blood pressure

Table 6. List of Other Systemic Agents Less Commonly Used for Treating Psoriasis

Biologic	Alefacept [344]	Etanercept [345] [346]	Infliximab [347] [348]	Adalimumab [349] [350] [351] [352]	Ustekinumab [353] [354]
Dose & Route & duration	15 mg. im weekely for 12 weeks	50 mg. sub cut 2x/wk for 12 weeks then once per week thereafter	3-10 mg/kg IV infusion over 2 hrs. at week 0, 2, 6, and every 8 weeks thereafter *	80 mg. given sub cut on week 0, 40 mg. given week one, then every other week *	For under 100 kg. body weight: 45 mg. sub cut week 0 week 4 then q 3 months. (over 90 kg body weight- 90 mg.)
Type of Rx course	Pulse of 12 weeks	Continuous	Continuous	Continuous	Continuous
Pre-Rx w/u	Baseline PPD	Baseline PPD US: Viral Hepatitis screen Monitor Deep Fungal where geographicallya ppropriate †	Baseline PPD US: Viral Hepatitis screen Monitor Deep Fungal where geographicallya ppropriate †	Baseline PPD US: Viral Hepatitis screen Monitor Deep Fungal where geographicallya ppropriate †	Baseline PPD US: Viral Hepatitis screen Monitor Deep Fungal where geographicallya ppropriate
Efficacy	28% achieved a PASI 75 at 12 weeks. After 2 courses the PASI-75 goes to 40%	49% achieved PASI 75% after 12 weeks (50 mg biw) vs. 59% at 24 weeks.	For 3 mg/kg body weight: PASI 75 was 72% at 10 weeks, and 88% for 5 mg/kg body wegight	At week 12, 53% achieved PASI 75 or >	PASI 75 ay week 12 was 66.7% for those taking the 45 mg dose; 75.7% who received one 90 mg dose.
Concurrent use of live vaccines	Not studied	Not recommended	Not recommended	Not recommended	Not recommended
Efficacious for treationg PsA	-	+	+	+	-/+

Safety	Lympho-penia, malignancy, serious infections (Contraindicated on HIV +)	Serious infections, exacerbation of demyelinating diseases like (MS & optic neuritis), pancytopenia malignancy, worsening of CHF, lupus like symptoms, +ANA, Improves glucose tolerance for diabetics lowering insulin needs	Infusion-related reactions, Serious infections, exacerbation of demyelinating diseases like (MS & optic neuritis), malignancy, or lymphoprilifera-tive disorders, worsening of CHF, lupus like symptoms, +ANA	Injection site reactions, exacerbation of demyelinating diseases like (MS & optic neuritis), cytopenias, malignancy, worsening of CHF, lupus like symptoms, +ANA	Clinical experience is short to compare with other biologics-serious infections, malignmancy, Reversible posrerior leukoencepha-lopathy syndrome, and cardiovascular events
Monitoring	$CD4^+$ T-cell counts every 2 weeks,	Annual PPD	Annual PPD	Annual PPD	Annual PPD
Long Term Data	Data on small number of patients	PASI response continues to improve to week 24. Restarting therapy after prolonged absence restores previous response. Long term safety profile established	Gradual loss of response is observed over time, especially in patients using the lower range	Loss of response was observed in 33 weeks if treatment was discontinued. Recent data shows efficacy with retreatment can restore initial gains	Not enough time has elapsed since its introduction for long term data
Pregnancy Category	B	B	B	B	B

* Low dose methotrexate (5-15 mg/week) often used to prevent antibody formation.
† Persons inhabiting or traveling through Ohio River Valley should be monitored for Histoplasmosis. Thoe inhabiting or traveling through San Joaquin Valley should be monitored for Coccidiodomycosis.

Table 7. Currently available Biologics to treat Psoriasis & Psoriatic Arthritis

9.1 Mortality in psoriasis

Mortality when it comes to psoriasis tends to occur in 3 major settings. The first tends to occur as a result of the specific co-morbidities commonly associated with severe psoriasis. Abuakara *et al* looked at a population-based cohort in the UK and found cardiovascular death as the major cause of mortality among patients with severe psoriasis. [355] Roth *et al* looked retrospectively over a 20 year period from 1965 to 1985 in France. Though the total number of patients documented to die from lethal psoriasis over a century reported in this review was 72, this number may be suspect since other causes may have lead to fatality. This study found patients whose cause of death was also related to co-morbidities including the metabolic syndrome, and visceral amyloidosis. Another group was identified with the most severe forms of psoriasis such as erythrodermic psoriasis, pustular psoriasis and psoriasis with polyarthritis. The third group was identified in which the cause of death was medication given to treat psoriasis. The largest number in this category was patients taking methotrexate. [356] Methotrexate should be used cautiously. Evidence is mounting that severe psoriasis along with the co-morbidities seen in this disease category may represent a risk factor for mortality. Well-controlled long term studies are needed to address this vital aspect.

9.2 Final comments

Certain intriguing aspects of psoriasis continue to haunt us as Nickoloff has stated on so many occasions. Psoriatic lesions in human skin have distinct clinical, histological and immunopathological features, of which not all can be reproduced in other experimental models such as mouse skin. Psoriatic skin can be restored grossly to clinical normal appearance, in spite of the fact that there may still be histological vestiges of disease activity found in clinically normal appearing skin. [357] In spite of the persistence, and often quite prominent inflammatory milieu, only rarely does one need to treat infection in psoriatic skin. Cellulitis, impetigo, viral or fungal and other parasitic infections are more commonly sequelae of atopic dermatitis, and are not generally seen in patients suffering with chronic psoriasis. Innate immunity as well as adaptive immunity are likely to play the role in maintaining the contrasting difference between these two disorders. [358] It is even rarer to record a progression to malignancy in specifically involved psoriatic skin. The interactions between the T_H1 and T_H17 networks needs further elucidation *vis a vis* the role IL-23 and IL-22 may play in this relation and its implication in the pathogenesis of psoriasis. As IL-23 has been found to promote tumor incidence and growth, this paradox needs to be resolved. A search for that elusive antigen which may be responsible to initiate and maintain the cascade of events that activates the cytokine network and leads to psoriasis continues. As more is learned about the intricacies of this pathogenesis process, it may become clear, that the sensitivity of the intercellular and intracellular interactions observed in this complicated web of events may be the result of overactive cellular forces, which may not require a specific antigenic trigger. Newer therapies are entering the arena.

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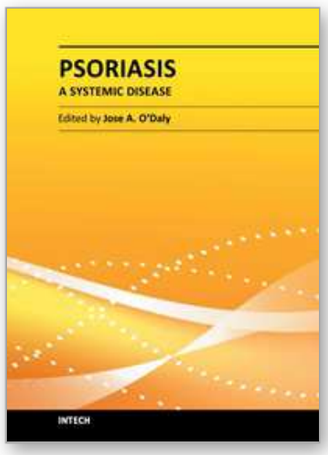

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The purpose of this book is to present a comprehensive analysis of Psoriasis, a disease that affects approximately 2-3% of humanity in all countries. Psoriasis existence is surveyed since the clay tablets of Assyrians and Babylonians 3.000-5.000 years ago, thru the middle ages, the renaissance, XIX and XX centuries.

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