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A comprehensive review of psoriasis

Pradip Kuma and PK Sahoo

Abstract
Psoriasis is a chronic, immune-mediated, inflammatory disorder characterized by erythema, redness, thickening, and scaling of the skin. Psoriasis is caused by the accelerated keratinocyte cell proliferation and dysregulation of the immune system. The cause of psoriasis is unknown, but it can be a genetic component. Several factors are thought to aggravate psoriasis. These include stress, excessive alcohol consumption, and smoking. The concept of the pathogenesis of psoriasis is based on the proliferation and differentiation of keratinocytes, recent studies have proved that the dysregulation of the immune system plays a critical role in the development of psoriasis. Immune cells release T cells, keratinocytes, neutrophils, and the cytokines, have a specific interaction with each other that is the core mechanism of the development of psoriasis. Trigger factors of psoriasis is also genetic, environmental and behavioral factors. The prevalence of psoriasis is estimated to range from 0.91% to 8.5% worldwide in adults. Clinically, psoriasis vulgaris is the most common subtype of psoriasis and affects approximately 90% of patients.

Keywords: Psoriasis, keratinocytes, cell proliferation, immune system, T-cells, neutrophils, cytokines

Introduction
Psoriasis is a non-infectious chronic skin disease affecting the keratinocytes, the cells that predominantly form the epidermis. In disease condition, the keratinocytes proliferate at ten times the rate of non-diseased skin cells and fail to mature properly, resulting in raised, inflamed, scaly red skin lesions known as plaques that can be itchy and painful [1]. Psoriasis is a long-term disease can affect all areas of skin, especially in scalp, nails and genital area. It also affects the area where the skin is folded like as underarms, insides the elbows and knees, under the breast. It can also because inflammation of the joints, which is known as psoriatic arthritis [2].

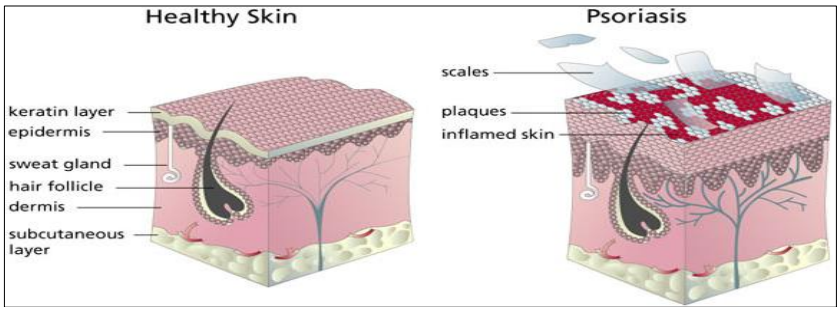

Fig 1: Difference between healthy skin and psoriatic skin.

Types of psoriasis
There are different types of Psoriasis.
1. Plaque psoriasis
2. Guttate psoriasis
3. Pustular psoriasis
4. Scalp psoriasis
5. Nail psoriasis
6. Inverse psoriasis
7. Erythrodermic psoriasis
8. Psoriatic arthritis

1. Plaque psoriasis (Psoriasis vulgaris)

Is the most common type of psoriasis and it gets its name from the plaques that build up on the skin. There tend to be well-denned patches of red raised skin that can appear on any area of the skin, but the knees, elbows, sacrum, scalp, hands, feet, trunk, and nails are the most common locations. There is also a white build up on top of the plaques, called scales. Plaque psoriasis symptoms may include skin pain, itching, and cracking. [3]

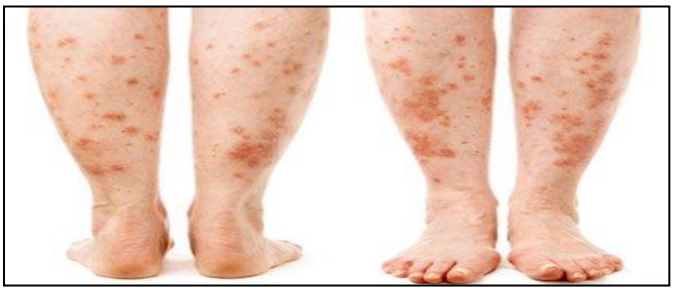

Fig 2: Picture of plaque psoriasis on the legs. Source: iStock.com

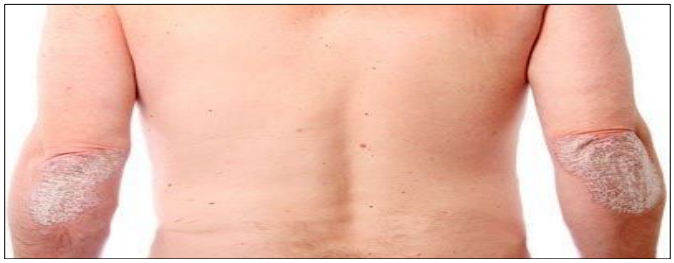

Fig 3: Picture of plaque psoriasis on the elbows. Source: Bigstock.com.

2. Subtypes of psoriasis vulgaris [4]

1. **Psoriasis gyrate-** in which curved linear patterns predominate.
2. **Annular Psoriasis**- in which ring-like lesions developed on the skin.
3. **Psoriasis follicularis**- in which minute scaly papules are present in at the opening of pilosebaceous follicles. Besides these, there are two distinct morphological subtypes of plaque psoriasis.
4. **Rupioid**- in which plaques are small (2-5 cm in diameter) and highly hyperkeratotic, resembling limpet shells.
5. **Ostraceous**- in which hyperkeratotic plaques with relatively concave centers, similar in shape to oyster shells are seen.
6. **Palmoplantarpustulosis (PPP): -** is relatively rare, with a prevalence of 0.01-0.5% (Lomholt 1963, Hellgre and Mobacken 1971). Upto 24% of PPP Patients Have psoriasis (Enfors and Molin 1971), which is much higher than the normal population prevalence of psoriasis. Painful sterile pustules on erythematous, scaly skin confined to palms and soles characterize PPP. It is commonly associated with tobacco smoking.

3. Guttate psoriasis

Guttate word is derived from the latin word gutta that means drop it is the second most common type of psoriasis, appears on the trunk, arm or legs, and usual for the condition to involve any areas of skin (scalp, face, or ears). It affects children and adult not more than 30 years old. Respiratory illness and viral infection are the common trigger factors. Guttate psoriasis isn't contagious. It can't spread to others through skin-to-skin contact. Spots often clear up with minor treatment. Guttate psoriasis is a lifelong condition for some, or it may appear later as plaque psoriasis. It is associated with a streptococcal throat infection [5].

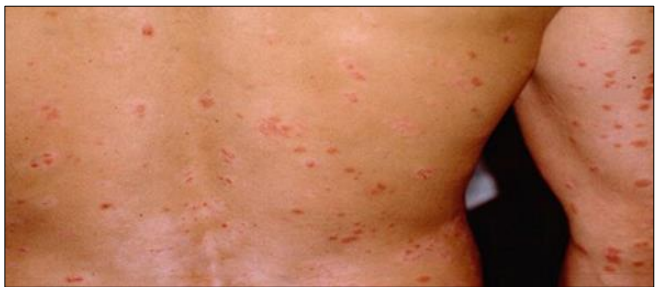

Image Source: Image courtesy of Hon Pak, M.D. and reprinted with permission from eMedicine.com, 2009

Fig 4: Guttateplaques.

4. Pustular Psoriasis

Pustular psoriasis is also known as "*von Zumbusch"* psoriasis, a rare disease, sometimes fatal form of psoriasis. Red skin filled with pus is the common problem of pustular psoriasis which can be itchy. It generally appears on the hand, feet, and fingertips of Young's, either in smaller sections or wide-spreadly. [6] Despite its appearance, it is not contagious. People often experience fever, chills, diarrhea, dehydration, increased heart rate, and other serious symptoms in this disease condition. It is the serious condition that's why needed to be admitted to the hospital as soon as possible. [7]

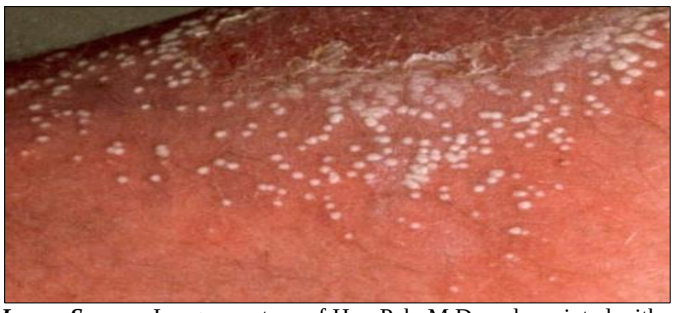

***Image Source*:** Image courtesy of Hon Pak, M.D. and reprinted with permission from eMedicine.com, 2009

Fig 5: Pustular psoriasis.

5. Scalp Psoriasis

Scalp psoriasis is a skin disorder that makes raised, reddish, often scaly patches, which can cause irritation and itching. It can affect the whole scalp, or one patch. It can be even spread to the forehead, back of the neck, or behind the ears. Symptoms of scalp psoriasis are scaling, dandruff-like flaking, dry scalp, and hair loss. [8]

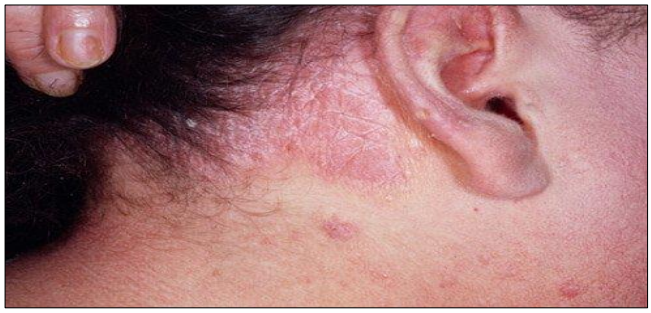

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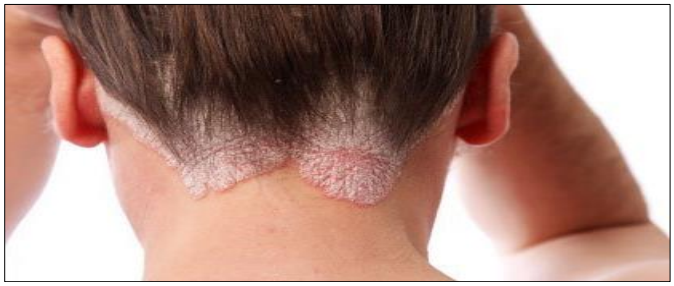
Fig 6: Symptoms of scalp psoriasis.



***Source*:** iStock.com.

Fig 7: Picture of scalp psoriasis.

6. Nail Psoriasis

Many patients with psoriasis have abnormal nails, commonly seen along with psoriatic arthritis. In psoriatic nails, distal onycholysis are formed that is a horizontal white or yellow margin due to a lifting of the nail from the nail bed. Onycholysis generally starts at the tip of the nail and extends toward the root. [9] A small pit is found in the nail plate that is often yellow and crumbly. It affects approximately 10-30% with skin symptoms, usually in the hands and feet. It is a fungal infection of nails. This condition may cause pain, redness, and irritation. [10]

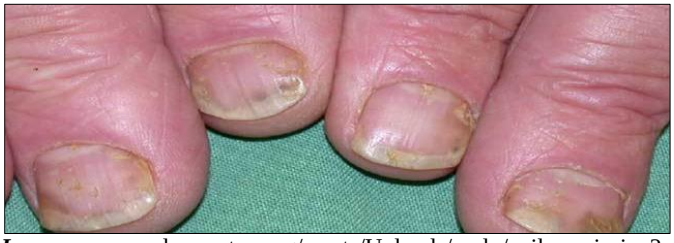


***Image source*:** dermnetnz.org/assets/Uploads/scaly/nail-psoriasis 2. jpg

Fig 8: Oncholysis

***Image source*:** dropbox.com/s/4y07mxzt8i7yu5m/nail-psoriasis-pitt%2315E14E0.jpeg?dl=0

Fig 9: Nail Pitting

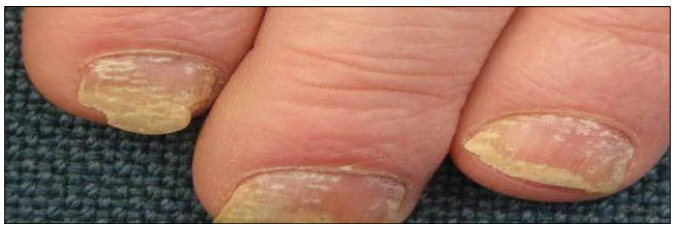


***Image source*:** dermnetnz.org/assets/Uploads/scaly/nail-psoriasis1. jpg.

Fig 10: Subungual hyperkeratosis

7. Inverse Psoriasis

Inverse psoriasis or intertriginous psoriasis is also known as "*Flexural"* psoriasis. It is an unusual type of psoriasis, localized in skin folds such as axilla, in the armpits, beneath the breasts, near the pelvis or in other skin folds. [11] Scaling is Generally not present but sometimes may be present in less amount, and the lesions appear glossy, smooth and bright red. It is commonly seen in obese patients. [12]

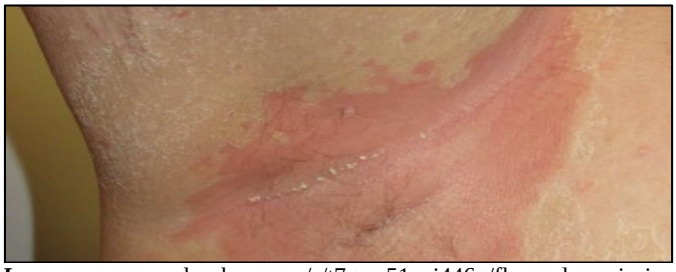


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Fig 11: Flexural plaques in underarms

8. Erythrodermic Psoriasis

It is a particularly severe form of psoriasis that leads to widespread, fiery redness over most of the body. This fiery redness may cause severe itching and pain, and make the skin come off in sheets. [13] It is a rare disease, only occurring in 3 percent of people who have psoriasis during their lifetime. It generally appears those peoples who have unstable plaque psoriasis. [14]

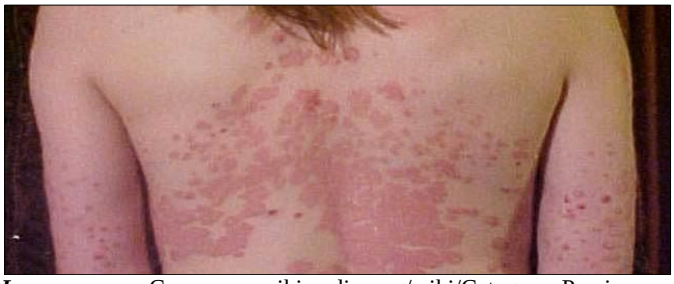
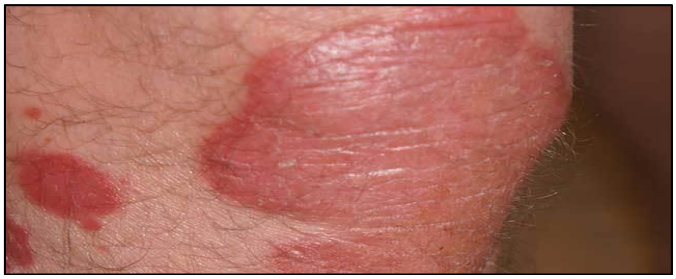


***Image source*:** Commons. wikimedia. org/wiki/Category: Psorias Is #/media/File: Schuppenflechte am _Knie. JPG

Fig 12: Erythrodermic plaques



***Imagesource*:** commons.wikimedia.org/wiki/Category:Psoriasis#/media/File:Schuppenflechte_am_Knie. JPG

Fig 13: Severe, diffuse erythrodermic psoriasis

9. Psoriatic Arthritis

Psoriatic arthritis is a chronic disease characterized by pain and swelling (inflammation) of the joints (arthritis). Psoriatic arthritis is characterized by inflammation of the joints as well as inflammation of the bones and tissues around the joints, associated with white-grey discoloration or scaly plaques of the skin. [15] A Sausage-shaped inflammation of the fingers and toes around the joints, known as dactylitis. Psoriatic arthritis is that cannot only cause inflammation of the skin, but in the eyes, heart, kidneys, and lungs as well. [16] Abnormalities of nails may also be present. The histopathological cause of psoriatic arthritis is unknown, but a

combination of genetic, immune, and environmental facts is likely involved. [17]

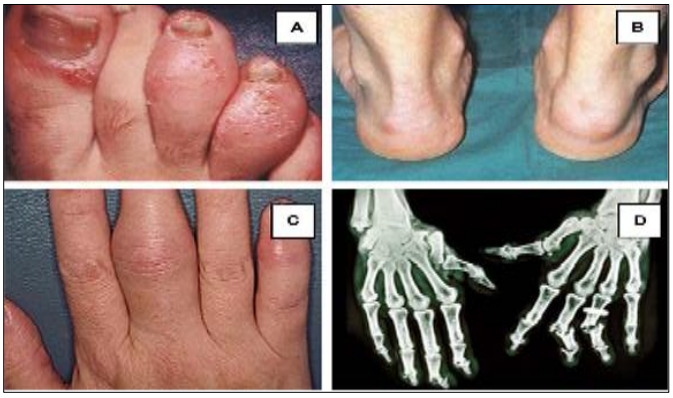


Fig 14: Symptoms that show psoriatic arthritis A, Dactylitis of third and fourth toes. B, Enthesitis of right Achilles tendon. C, Dactylitis of the middle finger. D, Radiograph of hands.

Types of psoriatic arthritis

There are five types of psoriatic arthritis:

- **Symmetric psoriatic arthritis.** It is associated with inflammation of joints on both sides of the body at the same time. It is similar to rheumatoid arthritis. About 50 percent of that type of psoriatic arthritis cases are found in India [18].
- **Asymmetric psoriatic arthritis:** This type of psoriasis often mild and appears in 35 percent of people with the condition. It's called asymmetric because it doesn't appear in the same joints on both sides of the body [19].
- **Distal psoriatic arthritis:** This type of psoriasis can cause inflammation and stiffness near the ends of the fingers and toes, along with changes in toenails and fingernails such as pitting, white spots and lifting from the nail bed (Onycholysis) [20].
- **Spondylitis:** This type of psoriasis can cause pain and stiffness in the spine and neck that are hallmarks of this form of psoriasis.
- **Arthritis mutilans:** It is the most severe form of psoriasis, arthritis mutilans affects only 5 percent of people who have the condition. It can cause deformities in the small joints at the ends of the fingers and toes, and destroyed them completely [21].

10. Epidemiology

Psoriasis is a chronic inflammatory disease of the skin which affects 2% of the world population but in the United States and Canada, the prevalence's as high as 4%. According to US study reports, the prevalence of psoriasis is very common in women than men but Indian reports suggest that the prevalence is twice more common in men and the earlieronset of disease is prior to 15 years. Psoriasis prevalent globally [22]. However, statistical studies show its variation among different geographic locations like the occurrence of disease is more common in colder north than in tropics. In a larger scale, the prevalence of psoriasis has been reported in a range between 0 to 11.8%. [23]

Psoriasis is a chronic inflammatory disease of skin and joints affecting around 0.5-1% ofchildren and 2- 3% of adults worldwide. General psoriasis has a bimodal peak of onset, and onset can peak at 20 to 30 years of age and 50 to60 years of age. Guttate psoriasis founds less than 30% of all total cases of psoriasis. It occurs in both genders equally, very common in children and adolescents than adults over the age of 30. [24]

Etiology [25]

- Idiopathic cause
- Genetic (HLA-cw6)
- Autoimmune reaction
- Infection (Streptococcus, HIV)
- Injury to skin
- Change in climate
- Medication (Lithium, Antimalarial Medications, B-blocker, Indomethacin)
- Stress
- Obesity
- Smoking
- Alcohol abuse
- Vitamin deficiency

Common Symptoms of Psoriasis [26]

- Raised, red, inflamed lesions
- Silvery scaly plaques
- Small, red, individual spots (More common in children and young adults).
- Dry skin that may crack and bleed
- Itching, burning, or soreness of the skin
- Pitted nails or separation from the nail bed

11. Pathophysiology

The Skin has three major segments dermis epidermis and subcutaneous fatty regions. The epidermis contains largely specialized cell called keratinocytes. These originate from the single layer of basal keratinocytes which divided continuously and give rise to cell migrates to the skin surface, during this process, they progressively differentiate into corneocytes which form a protective barrier [27]. The epidermis layer contains blood capillaries and lymphatic vessels. T-cells float around in the blood capillaries and play an essential role in cell- mediated immunity. These capillaries also contain of immune cells such as macrophages and dendritic cells. T-cells are immune effectors cells. Different types of theories exist regarding triggers of the disease process including an infectious episode, traumatic insult, and stressful life event, medications [28]. However, once triggered by the stress, genetic, autoimmune reaction, and medication, the basal skin cells.

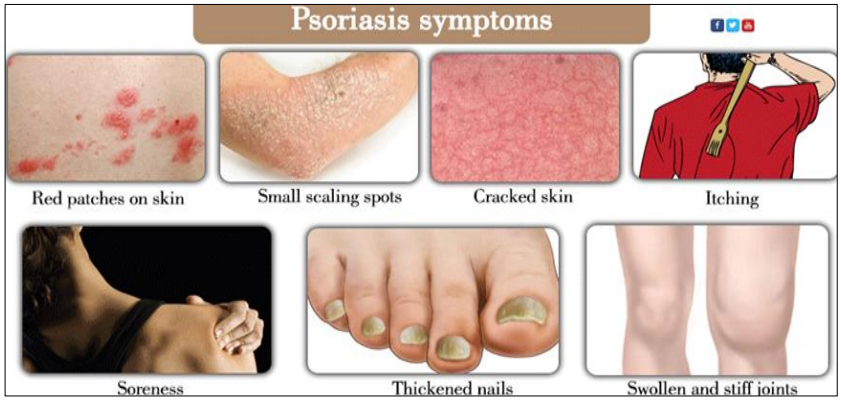


Fig 15: Psoriasis symptoms

Divided too quickly due to hyper activity of T-cells. Basal skin cells of epidermis layer are in-filtered by a large number of activated T-cells which appears to be capable of inducing keratinocytes proliferation. [29] These T-cells produces various cytokines interleukins-12, IL-17, IL-22, interferon-gamma, and tumor necrosis factor-α (TNF-α), causes vasodilatation and capillaries formation. Due to overproduction of these cytokines dysregulated inflammatory process takes places causes inflammation and redness of the skin. [30] T-cell hyperactivity and pro-inflammatory mediators (in this case IL-17/23) play a major role in the pathogenesis of psoriasis. Psoriatic cells may travel from basal skin cell layer of the epidermis to the stratum cornium (Skin surface) and be cast off in 3 to 4 days, in sharp contrast to the normal 26 to 28 days. In the affected skin of patients with psoriasis include vascular engorgement due to superficial blood vessel dilation and altered epidermal cell cycle causes epidermal hyperplasia and improper cell maturation. Fails to release adequate lipid which results in thickening of the epidermis and forms silver-white scales covering the skin. [31]

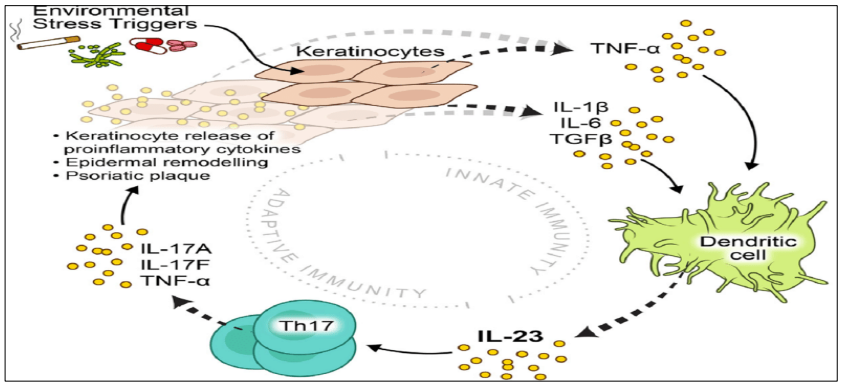


Fig 16: Process involved in Pathophysiology of Psoriasis

Diagnosis [32]

- Appearance of skin:-Thickening, Sliver white scales, Redness, Area of skin involvement varies with the form of psoriasis.
- Auspitz Sign:-Bleeding when Scales are peeled off.
- Ocular examination: Ectropion and trichiasis, conjunctivitis, conjunctival hyperemia, and corneal dryness.
- Musculoskeletal:-Swelling, Stiffness, pain, throbbing, or joints tenderness.

Testing [33]

There is no specific blood test for psoriasis but somemay include the following:

- Rheumatoid factor level (R_f): Negative
- Erythrocyte sedimentation rate (E.S.R..): Usually normal, except in pustular and erythrodermic psoriasis, where it may be elevated along with the white blood cell count
- Uric acid level: It may be increased in psoriasis (Especially in pustular psoriasis)
- Fungal studies: In cases of hand and foot psoriasis that seem to be worsening with the use of topical steroids or to determine if psoriatic nails are also infected with fungus

These are following baseline laboratory studies in patients being initiated on systemic therapies (eg, immunologic inhibitors):

- CBC count
- BUN and creatinine levels
- Liver function tests
- Hepatitis panel
- TB screening
- HIV testing
- Pregnancy test

Pharmacotherapy

Medications that are used in the treatment of psoriasis may include the following: [34]

- Topical corticosteroids:- Triamcinolone acetonide 0.025-0.1% cream (Kenalog Orabase, Kenalog topical, Pediaderm TA), beclomethasone 0.025-0.1% cream (Alphatrex, Beta Val, Dermabet).
- Ophthalmic corticosteroids:-Prednisolone acetate 1% ophthalmic (Pred Forte, Pred Mild, Omnipred), dexamethasone (Maxidex, Ozurdex).
- Intramuscular corticosteroids:-Triamcinolone (Kenalog, Aristospan).

- Intralesional corticosteroids:-It may be useful for resistant plaques and for the treatment of psoriatic nails.
- Coal tar 0.5-33%- It is used treat skin disease. (DHS Tar, Balnetar, Cutar, Polytar, Theraplex T).
- Keratolytic agents:-Anthralin (Dritho-Creme, Zithranol), Urea.
- Vitamin D analogs:-Calcitriol ointment (Vectical), calcipotriene (Dovonex, Sorilux, Calcitrene), Calciporiene/betamethasone topical ointment (Enstilar, Taclonex Ointment, Taclonex Topical Suspension).
- Retinoids:-Tazarotene aqueous gel and cream 0.05% and 0.1% (Tazorac Fabior, Avage, Acitretin.
- Antimetabolites:-Methotrexate (Trexall, Otrexup, Rheumatrex).
- Immunomodulators:-Tacrolimus topical 0.1% (Protopic), cyclosporine (Sandimmune, Neoral, Gengraf), alefacept, ustekinumab (Stelara).
- TNF inhibitors:-Infliximab (Remicade), etanercept (Enbrel, Erelzi, etanercept-szzs), adalimumab (Humira), certolizumab, golimumab, secukinumab (Cosentyx).
- Phosphodiesterase-4 inhibitors:-Apremilast (Otezla).
- Interleukin 12 &IL_23 inhibitors:-Ustekinumab, secukinumab, brodalumab (Siliq), apilimod.
- Inerleukin-17 A receptor inhibitors:-Ixekizumab.
- Phototherapy:-PUVA (Psoralen ultraviolet A), Excimer laser, Pulsed dye laser (PDA), Photodynamic therapy (PDT), Combination light therapy, Intense pulsed light (IPL).
- Artificial tears (Tears Naturale Forte, Bion Tears, Hypo Tears, Murine Tears).

Table: Drugs in the pipeline

S. N.	Drugs	Phase	MOA	Reference
1	Voclosporin	phase 3	Calcineurin inhibitor	35
2	AN2728	phase 1	PDE-4 inhibitor	36
3	Baricitinib	phase 2	JAK inhibitor	37
4	ASP015K	phase 2	JAK inhibitor	38
5	Ruxolintinib	phase 1	JAK inhibitor	39
6	CNTO 1959	phase 2	Anti-iL-23 (p19)	40
7	MK-3222	phase 3	Anti-iL-23 (p19)	41
8	SCH900222	phase 2	Anti-iL-23 (p19)	42
9	APG2305	phase 2	Anti-iL-23 receptor	43

12. Recent advancement in the treatment of psoriasis

Coal Tar has been used for nearly 2,000 years to treat skin diseases and specifically for psoriasis more than 100 years. They are often messy and smelly, but effective.

Goeckerman Therapy (1925)-A combination of coal tar and ultraviolet (UV) irradiation. Treatment course takes several weeks and therefor it is now less commonly used.

Methotrexate (1950s)-It is an antimetabolite drug which inhibits the cell growth and cell proliferation. Safe and highly effective for chronic plaque psoriasis, U.S. FDA approved this drug for common use in 1972. [44] Corticosteroids (1951)-Very effective as a short-term treatment. It is unsuitable for long-term use due to their growing risk of side effects. It decreases inflammation by suppressing the migration of polymorphonuclear leukocytes and reversing capillary permeability. [45] UVB Light (1970s)-It can clear mild cases of the disease. PSORALEN AND UVA LIGHT (PUVA) Possibly slightly more effective, although less convenient, than UVB therapy. [46] Vitamin D3 Analogues (1993)-Well tolerated and effective for long-term use with minimal side effects. Vitamin D3 analogues regulate skin cell production and development [47]. Acitretin (1996)-Effective for generalized pustular and erythrodermicpsoriasis, particularly in combination with UVB or PUVA therapy [48]. Alefacept (2003):- An immunosuppressant drug used to treat moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy [49]. Etanercept (Enbrel, 2004), a drug made by Amgen, was one of the earliest biologics on the market since it was first approved for the treatment of psoriasis in adults. U.S. FDA approved Enbrel for the treatment of chronic moderate to severe plaque psoriasis in children ages 4 to 17 in November 2016 [50]. Adalimumab was approved by the FDA in 2005 for the treatment of Ps A and three years Later received approval for treatment of psoriasis. So far, adalimumab has received licenses in only Europe (In 2015) for the treatment of children from four years of age. Adalimumab is a fully human monoclonal antibody of the IgG1 is otype that binds soluble and membrane-bound TNF- α like infliximab. [51] Remicade (2006, Infliximab)-Remicade is also used to treat severe or disabling plaque psoriasis (raised, silvery flaking of the skin). It is generally used when other medicines have not been effective. Infliximab is a chimeric IgG1 monoclonal antibody that binds to and neutralizes biological activity of TNF-α by binding soluble and membrane-bound TNF-α.

Humira (2008, Adalimumab)-Humira is a biological drug that can relieve pain and reduce inflammation in people with a number of autoimmune diseases. In July 2016, the Decision Resources Group (DRG) noted that Humira is continuing to gain popularity as a treatment for psoriasis. [52] Stelara (2009, Ustekinumab)-It is used to treat adults and children 12 years and older with moderate or severe plaque psoriasis and psoriatic arthritis who may benefit from taking injections or pills (systemic therapy) or phototherapy (treatment using ultraviolet light alone or with methotrexate). [53] Cosentyx (2015, secukinumab)-A biologic drug made by Novartis, used to treat moderate-to-severe plaque psoriasis in adults whose specialists have determined that systemic or phototherapy. It is also used to treat psoriatic arthritis and ankylosing spondylitis in adults who have not had an adequate response to other treatments [54]. In March 2016, the FDA approved Taltz (ixekizumab), a biologic drug manufactured by Eli Lilly, for the treatment of moderate to severe plaque psoriasis (fingernail Psoriasis) Taltz targets a cytokine, or pro-inflammatory protein, known as interleukin-17 [55]. In 2017, the FDA approved brodalumab (Siliq) and guselkumab (Tremfya) to treat moderate to severe plaque psoriasis. Ixekizumab (Taltz) was approved in 2016. All three drugs block the action of proteins called cytokines, which cause the inflammation that leads to psoriasis symptoms [56].

13. Challenges

Treatment of psoriasis for long-term remains a problem. Cumulative toxic effects are a limitation of classical treatment. Traditional topical therapy, phototherapy, and systemic therapy has low compliance among patients. The Past decade, treatment development has been based onmechanisms of pathogenesis. Treatment of psoriasis based on pathogenesis with a selective and focused action are likely to cause fewer side-effects. [57]

14. Limitations

Biologics do not cure Ps or Ps A but can relieve symptoms and may help to prevent further joint damage. Psoriasis treatment high cost (3000$ to 6000$ per month), a challenge especially for early intervention. Risk of infection is 20 to 40% higher than methotrexate,

CHF, MS, lupus. Most of the people improved after stopping treatment, indicates the biologic drug was the cause Cancers of the breast, colon, skin, and lymphoma. Long-term risks of the biologics have not been identified yet [58].

Summary

Psoriasis is a lifelong skin disease and currently there is no cure but various treatments can help to control the symptoms. Many of the most effective biological agents used to treat severe psoriasis carry an increased risk of significant morbidity including skin cancers, lymphoma, and liver disease. Psoriasis does get worse over time but it is not possible to predict who will go on to develop extensive psoriasis or those in whom the disease may appear to vanish. Individuals will often experience flares and remissions throughout their lives. To Controlling the signs and symptoms of psoriasis typically requires lifelong therapy.

Abbreviations

Ps A	Psoriasis arthritis
PASI	Psoriasis area severity index
TNF	Tumor necrosis factor
IL	Interleukin
FDA	Food and Drug Administration
I g	Immunoglobulin
I.M.	Intra-muscular

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