REVIEW ARTICLE

Psoriasis: An Overview of its Pathogenesis and Available Treatment Modalities

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Received: 25 Aug 2022 | Revised: 26 Oct 2022 | Accepted: 28 Oct 2022 |Published Online: 30 Oct 2022

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ISSN 2816-8119
Open Access

Citation
Salahuddin, Z., Khan, M. U. A., & Akhtar T. (2022). Psoriasis: An overview of its pathogenesis and available treatment modalities. *Albus Scientia*, *2022,* Article ID e221030, 1-5.

DOI
http://doi.org/10.56512/AS.2022.2.e221030

Competing interests
The authors have declared that no competing interests exist.

Abstract

Psoriasis is a chronic inflammatory and genetic disease that mainly involves skin with some complicated forms extending to other body systems. The disease is common with genetic predisposition as one of the major etiologies. It is known to occur because of immune system aberration involving helper T cells mainly and is thus treated on similar lines with most of the drugs belonging to immunomodulator class like steroids, calcineurin inhibitors, methotrexate, and various others like retinoids. Disease pathology has a new area of research advancement focused on oxidative stress. It has been suggested that reactive oxygen species have a considerable role in the cascade of pathological features. The disease shows relapses and remissions seldom showing a remarkable or complete recovery. A therapy which can completely resolve the cosmetic and other important symptoms is still a food for research. The dimensions of research have also been inclined to nano particles as treatment options over past few years. In this review, our key objective is to highlight the complexity and clinical diversity of this multifaceted disorder, its pathogenesis, and the potential of state-of-the-art treatment options.

Key words: *Chronic Skin Disease, Immunomodulators, Inflammation, Psoriasis, T Cell Mediated Immunity*

Introduction

Psoriasis is a well-studied chronic proliferative skin disease characterized by red plaques with silver or white scales and thickened epidermis with lesional areas easily differentiated from non lesional ones (Chuang et al., 2018). It is considered to be the result of aberration in the normal immune system of human body. Psoriasis confers significant burden to normal lifestyle with reduction in normal healthy responses. The keratinocytes grow rapidly and form scales and itchy patches. These scaly patches are often seen on elbows, scalp , knees and can last for several months or years (Lowes et al., 2014). Histologically epidermal hyperplasia is seen overlying inflammatory cells like dendrites and macrophages. Extensively dry skin is associated with bleeding. Besides skin, psoriasis has also been seen affecting the nails, eyes, joints, and other body parts. (Alexis & Blackcloud, 2014).

Psoriasis shows periodical episodes of relief and relapse. It is mostly the relief of symptoms which can be achieved somehow due to suppression of immune response to the disease. Most common risk factors include family history, stress, infection, and smoking (Bessar et al., 2016). The risk of co-morbidities like hypertension, ischemic heart disease, type 2 diabetes mellitus, hyperlipidemia, gastrointestinal disturbances, and chronic kidney disease has been found to be more in psoriatic individuals as compared to normal population. Also, these patients are considerably prone to depression, stress and anxiety owing to their disease (Emre et al., 2013). Alcoholics also have more chances of developing the disease as compared to non-alcoholics (Szentkereszty-Kovács et al., 2021). Moreover, the consumption of alcohol and smoking also leads to exacerbation of disease according to some studies (Ayala-Fontanez et al., 2016).

Extensive research work done in the past has significantly established pivotal involvement of T cell/ adaptive immunity in pathogenesis of psoriasis with major consent on the involvement of IL23/Th17 axis. Evidence also suggests significant genetic predisposition towards involvement of disease (Schön & Erpenbeck, 2018).

In the recent years, like other inflammatory diseases psoriasis is also believed to be the end result of oxidative stress (Baz et al., 2003). The current direction of research is towards establishing various mechanisms at molecular or epigenetic level involved in the pathology of psoriasis. Available therapies depend upon the severity of the disease, magnitude of area involved and co-morbidities or individual patient factors. For mild cases topical corticosteroids, anthracin, retinoids, calcineurin inhibitors and salicylic acid are used while severe cases have shown to respond to systemic steroids, methotrexate, and cyclosporine in common practice. The symptoms are resolved most of the times with these therapies however frequent relapses are seen. None of the drug offers complete or long-term recovery when used alone (Nijsten. Et al., 2005).

Prevalence

Each year 2-4% of the global population gets affected with psoriasis with disease incidence varied from 0.09 to 11.4% in different countries and races (Michalek et al., 2017). High prevalence of psoriasis has been found in areas away from the equator (Chandran & Raychaudhuri 2010). It has not been reported in indigenous people of Latin America, Samoa, and New Zealand populations., Whereas a high prevalence of psoriasis has been reported in in Kasachy population (12%). In Asian countries its prevalence is 0.4% in China, 0.19-0.24% in Taiwan, 0.3–1% in Japan, and 0.44-2.8% in India (Danielsen et al., 2013), while in in West African and American black population its reported prevalence is 0.3–0.7% and 0.7%, respectively (Alexis & Blackcloud, 2014). Any individual can suffer from psoriasis regardless of age leading to significant physical, psychological, and social constraints. Prevalence is more in males as compared to females (Parisi et al., 2013).

Stages and Types

In general, the disease presents as red scaly patches over extensor surface of extremities, scalp, back of trunk, groin, and other parts of the body. The patients complain of itchy skin which often leads to bleeds as a result. The lesions may extend to eyes, nails, joints, and spine as well (Alexis & Blackcloud, 2014).

Epidermal hyperplasia, lymphocytic infiltration and neovascularization are the hallmark of histology of a psoriatic skin. Histologically it can be divided into an early stage with dilated blood vessels and lymphocytic infiltration of dermis. Later epidermis starts to thicken and incompletely differentiated keratinocytes are seen due to rapid proliferation. Advanced stage is characterized as thickening of stratum spinosum and epidermal psoriasiform hyperplasia (Kadam et al., 2010). At this stage infiltration of inflammatory cells further increases and T lymphocytes can be seen embedded between keratocytes (Nickoloff et al., 2000).

Plaque psoriasis, which is also called psoriasis vulgaris is characterized by red raised patch covered with white or silver accumulation of dead skin cells. It is very itchy and painful affecting mostly the trunk region and extensor surfaces of limbs. It has two morphological divisions as described (Burden & Kirby, 2016).

Pustular psoriasis has blistering white pustules most commonly seen on soles of feet and palms. Erythrodermic psoriasis has severe erythema and skin shedding while guttate psoriasis appears as red dot like spots on different areas of skin, commonly involving trunk and limbs. It is mostly seen affecting children and adolescents. Guttate psoriasis is triggered by group A streptococcal infection. Another important type is inverse psoriasis which has shiny smooth red lesions and usually occurs in body folds like axillary, intergluteal and genital folds (Syed & Khachemoune, 2011). Psoriasis is not limited to skin only. In advanced cases it also invades joints leading to psoriatic arthritis or nails (nail psoriasis). Out of psoriatic patients, more than 50 % develop nail psoriasis while almost 40 % of them have psoriatic arthritis (Ritchlin et al., 2017).

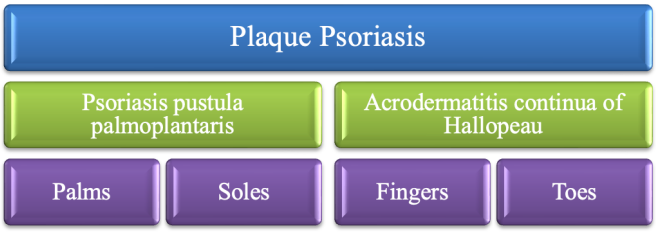

Figure 1: Types of Plaque Psoriasis

Role of Genetics

Evidence based research work has highlighted crucial role of genetics in possibility of developing psoriasis. The development is more common in first degree and second-degree relatives. Similarly increased risk of psoriasis development is seen in monozygotic and dizygotic twins. The most common locus involved in the formation of psoriasis is PSORS1 located on chromosome 6p21 within major histocompatibility complex corresponding to HLAcW6. HLAcW6 has a very strong association with psoriasis as documented in various research works (Talamonti et al., 2013). Other gene regions (PSORS2 (17q25), PSORS3 (4q34), PSORS4 (1q), PSORS5 (3q21, PSORS6 (19p13), PSORS7 (1p) PSORS8 (16q12-13), PSORS11 (5q31.1-q33.1), PSORS12 (20q13), and PSORS13 (6q21)) related to psoriasis distribute to different chromosomes (Barker, 2001).

Pathophysiology

Psoriasis has multifactorial pathophysiology with predisposing factors as described above. It is considered to be immunologically mediated inflammatory condition with involvement of cells like T lymphocytes, keratinocytes, Langerhans' cells, macrophages, antigen presenting cells and natural killer cells. Individuals expressing certain HLA class I antigens, particularly HLA-Cw6 have been found to have an association with an early onset and also positive family history for the disease. Different cytokines like TNF α, IL 17, IL 23, and IL 6 has been reported to be upregulated under diseased condition. Release of antimicrobial peptides (AMP) like LL37, S100, β defensins from keratinocytes is also reported (Das et al., 2009). These AMPs interact with body's immune system leading to the production of IFN1 which triggers helper T cell differentiation.

Dendritic cells and macrophages are attributed for the release of IL 23 and IL6 in the skin, which helps in the differentiation of TH1 and TH17 cells, that stimulates the release of IL 17, IL 21, and IL 22 (Schön & Erpenbeck, 2018). These cytokines later

play their role to secrete cytokines and other inflammatory mediators from epidermal cells (Ayala-Fontanez et al., 2016). These chemokines further attract and activate more cells of innate immune system leading to an onset of a vicious inflammatory cycle where IL 23 and IL 17 play a key role in activation of JAK/STAT pathway (Tonel et al., 2010). However, despite much of research directed towards it, the pathogenesis of psoriasis still remains a question of debate and mystery.

Recently, it has been reported that a high levels of reactive oxygen species due to compromised antioxidant system plays a key role in the psoriasis pathogenesis (Lin & Huang, 2016). Due to significant exposure of the skin to the UV radiations and other environmental factors skin becomes the potential target for an oxidative injury (Capon, 2017). Nitric oxide generated through UV radiations plays an important role in melanin production and erythema (Panich et al., 2016). Also, the plasma membranes of the skin cells in psoriatic lesions have increased expression of arachidonic acid which is required for the synthesis of malondialdehyde. Malondialdehyde is the end product of lipid peroxidation which is one of the processes involved in oxidative damage (Şikar Aktürk et al., 2011). Increased levels of malondialdehyde in psoriasis patients support the fact that involvement of oxidative stress cannot be ruled out . Moreover, there is decrease in activity of erythrocyte superoxide dismutase and catalase. Increased H2O2 accumulation is the cause of reduced superoxide dismutase activity and increased levels of catalase. Catalase degrades H2O2 into water and oxygen. Erythrocyte GSH peroxidase is also reduced which has a protective role against oxidative stress (Lin & Huang, 2016).

Association of Psoriasis with other Autoimmune Diseases

Association of psoriasis with other autoimmune diseases is an area of interest for research these days. Earlier studies have shown a higher incidence of autoimmune diseases in psoriatic patients than seen in the general population. A retrospective study conducted from January 1, 1980, to June 1, 2011, had shown that the major autoimmune disorders associated with psoriasis included Rheumatoid Arthritis, celiac disease, Inflammatory Bowel Disease, Celiac Disease, multiple sclerosis, Systemic Lupus Erythematosus, Sjogren's syndrome and alopecia (Ayala-Fontanez et al., 2016).

Treatment

Topical and systemic corticosteroids act by suppressing immune system and reduction of inflammation. Commonly used steroids include dexamethasone and prednisolone (Paul et al., 2011). Their long-term use results in adverse effects like Cushing syndrome, hyperglycemia, salt and water retention and hyperlipidemia. Owing to the adverse effects of steroids, the attempts to explore new drug moieties never fade off. Calcineurin inhibitors also work by suppressing immune system (Behnam et al., 2005). Commonly used one in psoriasis is cyclosporine. Vitamin D therapy helps to keep the skin healthy and various trials have supported their role in improvement. For the treatment of mild to moderate psoriasis, vitamin D analogues are used. After 4-6 weeks of treatment, between 30% to 50% of the patients treated showed a significant improvement or had full clearance, according to the global assessment of efficacy. Vitamin D analogues bind to the intracellular vitamin D receptor; this binding has subsequent effects, including the direct control of genes involved in the proliferation, inflammation, and keratinization of the epidermis. Currently, calcipotriol, tacalcitol, and calcitriol are the three vitamin D analogues used to treat psoriasis (Ayala-Fontánez et al., 2016).

Retinoids, like acitretin are vitamin A derivatives which work by inhibiting excessive keratinization and uncontrolled growth of skin cells. Oral retinoids have been used as a treatment for psoriasis since the early 1980s. They can be administered alone or in combination with UV light treatment, the latter has been shown to be more effective in patients with psoriasis vulgaris. Phototherapy also slows the growth of skin cells. Mostly ultraviolet b is used for this therapy (Panich et al., 2016).

Methotrexate has anti-inflammatory, immunosuppressive and anti-proliferative properties due to inhibition of dihydrofolate reductase. This leads to low production of folic acid hence inflammatory cells are not synthesized and immune system is suppressed however methotrexate causes blood dyscrasias as adverse effect. Monoclonal antibodies also target the immune cells. TNFα inhibitors include etanercept, adalimumab, certolizumab and infliximab. As described earlier, the TNF α has significant role in the pathology of psoriasis hence drugs targeting it are good candidates (Imafuku et al., 2018).

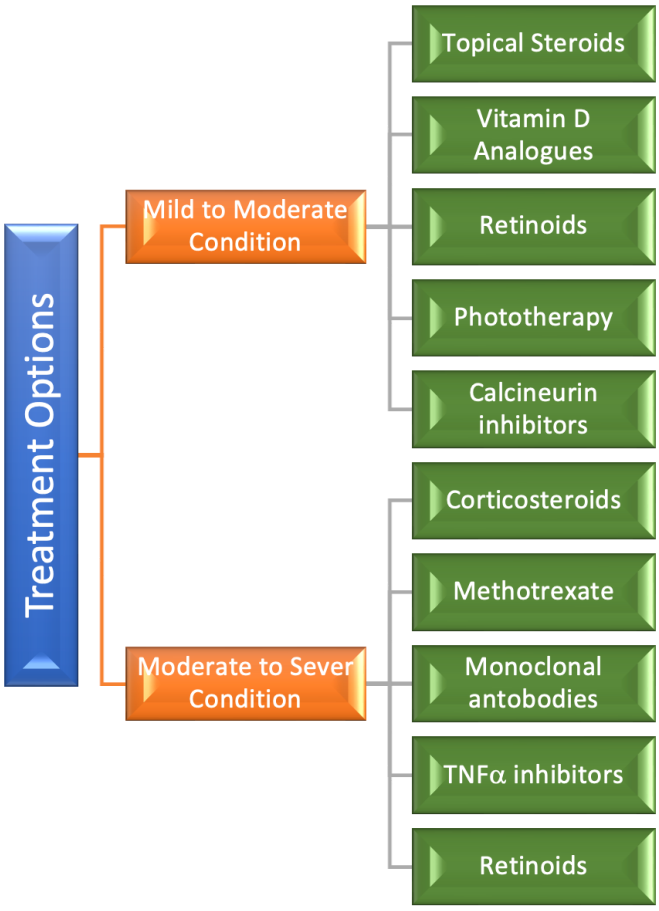

Figure 2 : Available treatment options for Psoriasis

The use of nano particle technology offers a better approach to treatment of disease and research in the respective area is at its peak. The data on human study is limited however short-term use has been extensively tried and is safe as of found till date.

Nano particles have increased skin retention and decreased systemic absorption as their major hall marks in the treatment choice of psoriasis (Sonawane et al., 2014). They are safe and offer sustained release as well. Nanotechnological approaches are worked upon to achieve complete cure of the disease which is not possible with existing modalities. These nano particles including carriers like liposomes, transferosomes, niosomes, micelles, dendrimers etc. can be given through topical, dermal, or systemic routes (Kim et al., 2007).

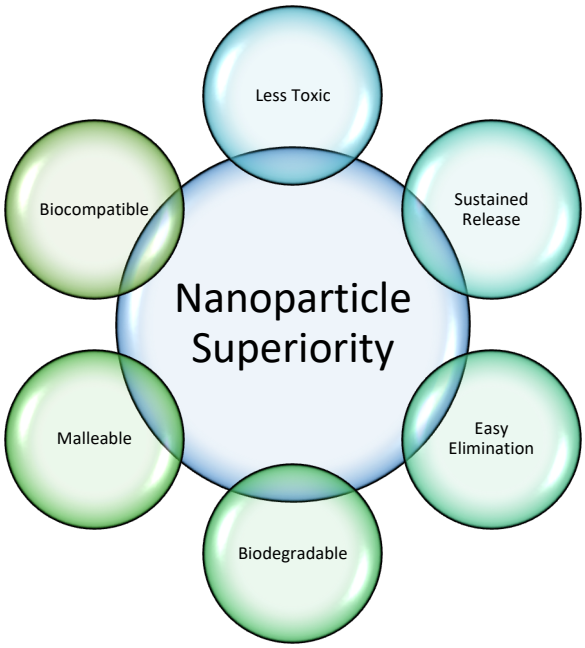

Figure 3: Merits of Nanoparticles

Area of Research

Future research is focused on extensive work up of pathophysiology of psoriasis with some insight of epigenetic modulation which involves gene modification without changing gene sequence regarding treatment. Various inflammatory pathways are the areas of interest for various researchers. The benefit of this idea will be related to discovery of new treatment modalities as till date efficient recovery from psoriasis has still a long way to go.

Authors' Contributions

The authors confirm substantial contribution to the review article. ZS and TA conceptualized and prepared outline of the review article. ZS and MUAK wrote the first draft. All the authors contributed to manuscript revision and approved the final version of the article.

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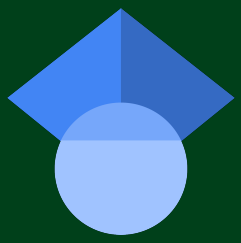


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