IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Human Journals
Review Article
May 2021 Vol.:21, Issue:2

Psoriasis Experimental Models and Treatment

IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

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Submitted: 25 April 2021
Accepted: 02 May 2021
Published: 30 May 2021

HUMAN JOURNALS
www.ijppr.humanjournals.com

Keywords: Psoriasis, Experimental Models and Treatment, autoimmune disease

ABSTRACT

Psoriasis is the most common autoimmune disease in men, characterised by raised cutaneous plaques with clear scaling and variable erythema that range from focal to coalescing. While the pathogenesis of psoriasis is unclear, the underlying mechanisms include a complex interplay between epidermal keratinocytes, T lymphocytes, and other leukocytes (including dendritic cells and other antigen presenting cells [APCs]), as well as vascular endothelium. With the addition of many relatively loosely described spontaneous murine mutant models, psoriasis models can be narrowly divided on the basis of the pathogenic mechanisms that interact to induce psoriasis. Aside from spontaneous mutant models, there are genetically modified (transgenic and knockout with modification of the epidermis, leukocytes, or endothelium) and induced psoriasis murine models (either by immune transfer or by xenotransplantation of skin from psoriatic patients). *In vitro* human epidermal models, in addition to murine models, have recently become more common. The latest treatments slow the progression of the disease and reduce its symptoms, but there is no cure. This article has examined all of the currently available treatments for the treatment of psoriasis. With a deeper understanding of immune pathogenesis, the goal of therapy has moved to a more targeted, immunologically guided approach. This paper discusses a variety of target-based therapies, such as biologics, that target cytokine mediators and receptors, resulting in a more precise and effective therapeutic outcome. **Summary** - The aim of this review is to summarize and present scientific evidence on Experimental models and pharmacological/non-pharmacological treatment of psoriasis. With the assistance of PubMed, Google Scholar, Springer, and other online tools, data was gathered.

LIST OF ABBREVIATIONS

PS	Psoriasis
NK	Natural killer cells
EGF	Epidermal growth factor
CsA	Cyclosporine A
IFN	Interferon
IMQ	Imiquimod
pDC	Plasmacytoid dendritic cells
DC	Dendritic cell
IL	Interleukin
UV	Ultraviolet
UVB	Short wave ultraviolet B
UVA	Long wave ultraviolet A
TNF	Tumour necrosis factor

INTRODUCTION:

Psoriasis is a recurrent persistent relapse of inflammatory cutaneous skin disease characterized by thickened skin patches and caused by excessive proliferation of keratinocytes, vascular hyperplasia and inflammatory cell infiltration into the dermis and epidermis, leading to a substantial worsening of the quality of life of patients affected. The incidence ranges between 1 and 4% of the world's population.[1]

Innate immunity elements, such as dendritic cells, natural killer (NK) T cells, neutrophilic granulocytes and macrophages, as well as T lymphocytes, CD8+ and CD4+ (T helper 1, Th1; Th17), generate acquired immunity, contributing to psoriatic lesion immune response.[2]

Experimental models used for psoriasis

A strong *in vivo* laboratory tool that enables scientists to systematically research the genetic and immune processes leading to psoriatic disease is the ability to model human

disease in animals. These models can be divided into three main types: acute (inducible), transgenic (genetically engineered) and xenograft (humanized).

Spontaneous mouse models:

A progressive Papulosquamous skin disease is demonstrated by the flaky skin (Ttc7fsn/Ttc7fsn) mouse. There are pits, striations, and outward expanding protrusions in the hair shafts of these rodents. The skin displays neutrophil intraepidermal invasion, increased levels of the epidermal growth factor (EGF) receptor and, surprisingly, a positive Koebner reaction after tape-stripping that resolves after 6 weeks of treatment with oral, but not topical, cyclosporine A (CsA), topical EGF, or UVB exposure Keratinocytes of the Flaky skin mouse have mitochondrial aberrations and homosexual aberrations.[3]

Redness, alopecia, scaling, and extreme pruritus are all signs of spontaneous chronic proliferative dermatitis mutation (cpdm/cpdm). Epithelial hyperproliferation is followed by eosinophils, macrophages, and mast cells invasion, but just a few T cells. Corticosteroid therapy could partially reverse the phenotype, but CsA was completely ineffective. The use of topical calcipotriene reduced cell proliferation while having no effect on epidermal thickness.

Because of a mutation in the stearoyl coenzyme A desaturase-1 (Scd1) gene, homozygous asebia (Scd1ab/Scd1ab) mutant mice are thin, hunched, and have hypoplastic sebaceous glands. Adult homozygotes grow scaly skin and alopecia generalis. The epidermis is thickened histologically, with swollen intercellular spaces and disproportionately long hair follicles reaching into the deep subcutis at a sharp angle. The dermis of the mutant mice has thickened, with increased vascularity, cellularity, and prominent fibroblasts. Mast cells and macrophages abound in the dermal cellular infiltrate, but T cells and neutrophils are missing.[4]

Genetically engineered (transgenic) models

Mice with specific gene alterations resulting in overexpression or loss/knockout (KO) of a specific protein are known as genetically modified or transgenic models. Traditional transgenic mice, in contrast to acute model systems, have gene alterations that are present at birth and affect all cell types throughout the body Advanced laboratory techniques now enable the development of transgenic mice with genetic

modifications restricted to a specific tissue type or cell population, all under the regulatory control of a specific gene promoter (e.g., keratin 5 or 14) and/or a gene expression modulator like tetracycline/doxycycline or tamoxifen.[5]

Whole-body knockout mice have the disadvantages of being labour intensive, time consuming, costly, and often resulting in embryonic or prenatal death. Single gene mutations are also not characteristic of complex, mutagenic disease states like psoriasis and do not constitute genetic alterations found in human tissues. The ability to decide which cell populations or tissues are predominantly responsible for an observed phenotype is also limited when a gene is altered in the body.

Xenograft (humanized) models

Psoriasis xenotransplantation mouse models are an alternative to transgenic mice. When mice are engrafted with human tissues or cells, xenograft or humanised models are developed. Nonlesional or lesional psoriatic skin is transplanted on the backs of immunocompromised mice, such as severe combined immunodeficient or AGR129 mice, in preclinical psoriasis studies. Due to the absence of B and T lymphocytes, both model systems allow engraftment without tissue rejection, but AGR129 mice also lack type I(A) and II(G) IFN receptors as well as Rag-2/, resulting in decreased natural killer cell activity. As a result of the expansion of resident immune cell populations present in donor skin, transplanted human tissues grow into psoriatic plaques.[6]

Imiquimod-induced psoriasis in mice:

Aldara cream, which contains 5% imiquimod (IMQ), was first used to treat skin changes caused by the human papillomavirus. IMQ was also successful in the treatment of some types of cancer, with tumour regression occurring in up to 90% of cases. Psoriatic lesions appeared in patients using the Aldara cream, both in the area of application and at remote, unaffected locations. IMQ is a ligand for macrophages, monocytes, and plasmacytoid dendritic cells' Toll-like receptors (pDCs). As a result, it leads to high immune system activation (e.g., enhancing Th1 response or increasing the Langerhans cells migration). Researchers have developed a targeted, induced mouse model of psoriasis based on these mechanisms (Ps). The medication (5 percent Aldara) was applied to the back skin of BALB/c mice at a dosage of 62.5 mg daily for 5–6 days. Regular application of IMQ caused the development of skin lesions similar to psoriatic

plaques, just as it did in humans. Increased epidermal proliferation, erythema, altered vascularity, and impaired keratinocyte differentiation followed these changes (caused by the accumulation of neutrophils in the epidermis), the influx of CD4+ T cells, CD11c+ dendritic cells, and pDCs to the skin during neoangiogenesis. Importantly, IMQ has been shown to induce the expression of the IL-17A, IL-17F, and IL-23 genes in the epidermis. Phenotypic changes are partly dependent on the involvement of T lymphocytes, and the disease does not evolve in mice lacking IL-17 and IL-23 receptors, indicating that the IL-23/IL-17 axis plays a critical role in Ps.[7]

IL-23 induced psoriasis model:

Antigen-presenting cells contain IL-23, which is made up of the p19 and p40 subunits. IL-23 is needed for the differentiation of naive lymphocytes into Th17 and Th22 cells, both of which are involved in the progression of skin inflammation. 1 µg IL-23 injected intradermally into mouse skin stimulates the development of IL-19 and IL-24, which affect keratinocyte differentiation and proliferation through a TNF-dependent mechanism (but not IL-17A). Many histological changes arise as a result, including follicular hyperplasia, parakeratosis and acanthosis. With the influx of CD4+ lymphocytes, dendritic cells, neutrophils, and macrophages, the skin of these mice becomes erythematous. This mouse model displays a wide variety of Ps symptoms, highlighting the role of IL-23 in the development of psoriatic plaques.[8]

Mouse tail model:

The mouse-tail model is based on the induction of orthokeratosis in areas of the adult mouse-tail that would normally be parakeratotic. This is widely recognised as a screening tool for determining drug anti-psoriatic activity. Topical treatment of a mouse tail with anti-psoriatic drugs improves orthokeratotic cell differentiation in the epidermal scales, which is the basis of this process. In an animal model, this trait was used to test drug efficacy directly. For two weeks, drugs were applied topically once a day, five days a week. The animals were sacrificed two hours after the last injection, and longitudinal portions of the tail skin were made and prepared for histological analysis (hematoxylin- eosin staining). The number of scale regions with a continuous granular layer was counted and expressed as a percentage of the total number of scale regions per segment as an indicator of orthokeratosis. The rise in the proportion of orthokeratotic regions is an indicator of drug use.

UV radiation induced psoriasis in rats:

A total of eight Wistar rats weighing about 120 g were used, with each group consisting of two rats. Hair removal cream was used on the dorsal skin to remove hairs (Veet). In groups 2, 3, and 4, a 10% of the body surface area was irradiated with UV light (385 nm) for 15, 30, and 45 minutes at a vertical distance of 20 cm. The first group was used as a control group (No radiation). Following irradiation, rats were observed for any changes in the irradiated skin, the presence of skin lesions, and other behavioural changes.[9]

TREATMENT

Non pharmacological treatment:

- **Diet**

A diet rich in eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) can help people with psoriasis or psoriatic arthritis (DHA). The severity of psoriasis tends to be reduced by a low-calorie diet. Consumption of cold water, fish (preferably wild, not farmed) such as salmon, herring, and mackerel, extra virgin olive oil, legumes, vegetables, fruits, and whole grains, and avoidance of alcohol, red meat, and dairy products are among the diet guidelines (due to their saturated fat).[10]

- **Phototherapy**

It is prescribed for patients that do not respond to topical treatments or who have psoriasis plaques that cover 20% or more of their body surface. Psoriasis has long been treated with UV phototherapy, which involves exposure to sunlight. The most powerful UVB wavelengths are 311–313 nanometers. In patients with moderate-to-severe psoriasis, UVB radiation combined with coal tar (Goeckerman therapy) or anthralin (Ingram regimen) has been shown to be successful Ultraviolet radiation. The combination of UVA and systemic psoralens (PUVA therapy) has been shown to be highly successful in removing skin lesions, but both of these therapies need ongoing maintenance and raise the risk of skin cancer. Broadband UVB therapy is less effective than narrowband UVB therapy (311-313 nm). Redness, scratching, dry skin, wrinkled skin, freckles, and skin cancer are all side effects.[11]

Pharmacological treatment

- **Topical therapy**

Corticosteroids – They're the most commonly prescribed psoriasis drugs for mild to moderate psoriasis. They minimise inflammation and itching by slowing cell turnover and suppressing the immune system. Clobetasol propionate 0.05%, amcinonide 0.1%, betamethasone dipropionate, betamethasone valerate as 0.1%, 0.12%, and 1%, halcinonide 0.1%, desoximetasone 0.25%, and mometasone furoate are some of the corticosteroids used.[12]

Vitamin D Analogues – In the long-term treatment of psoriasis, vitamin D analogues (calcitriol and calcipotriene) have emerged as promising alternatives to topical corticosteroids.[13]

Anthralin (Dithranol) – It comes from the Araroba tree, which can be found in South America. It triggers the release of reactive oxygen species, which inhibits hyperproliferating keratinocytes and leucocyte transformation. It is applied to the scalp in rising concentrations (0.1% to 3%).

Coal Tar – It is one of the oldest topical treatments for the treatment of psoriasis, and it is used as a monotherapy as well as in conjunction with other topical agents, systemic agents, and phototherapy.[14]

Retinoid - Oral retinoid is mostly used as a maintenance treatment in chronic plaque psoriasis, with a focus on pustular psoriasis. It may also be used in erythrodermic psoriasis, but it appears to be less effective. It is thought to regulate DNA activity in skin cells and reduce inflammation.[15]

Methotrexate- Is an immune suppressant and antimetabolite that is one of the most effective and inexpensive treatments for psoriasis.[16]

Cyclosporine- Is an oral therapy for moderate-to-severe psoriasis that is very successful. It binds to cyclophilin, inhibits calcineurin, and thus causes immunosuppression by preventing T-cell activation downstream.[17]

- **New drug targets:**

Anti TNF-α agents: These are molecules that block the TNF-a receptors or act on the tumour necrosis factor (TNF-a). Etanercept, Certolizumab pegol, Adalimumab, and Golimumab are some of the anti-TNF-a drugs that have been produced so far.[17]

IL-23 and IL- 12 inhibitors: Inhibitors of IL-23 and IL-12, such as Ustekinumab andApilimod, stop the immunological cascade by blocking the subunits of IL-23 and IL-12. Ustekinumab, Guselkumab, and Apilimod are inhibitors of IL-23 and IL-12.[18]

Fusion protein inhibitor: Alefacept is the only drug in this class that has been approved by the FDA.

Janus kinase (JAK) inhibitor: Tofacitinib is an FDA-approved oral selective Janus kinase inhibitor for the treatment of rheumatoid arthritis (RA), but it is also being tested for the treatment of psoriasis and is currently in phase 3 trials.[19]

Phosphodiester-4 inhibitor: Apremilast is an FDA-approved oral medicine for the treatment of psoriatic arthritis and mild to extreme plaque psoriasis.

Anti CD-6 (cluster of differentiation) monoclonal antibody: Itolizumab is a drug that inhibits T cell signalling and differentiation into Th1 and Th17 cell.[20]

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