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DRUG SCREENING METHODS FOR PSORIASIS PLAQUES - A REVIEW

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ABSTRACT

Psoriasis is an autoimmune inflammatory skin disease characterised by red plaques with silver or white multi-layered scales and a thickened acanthotic epidermis that is markedly demarcated from the adjacent non-lesion skin in affected individuals. Its pathogenesis is multifactorial; genetic, immunological and environmental factors influencing the disease. The major lacuna in designing a dermatological disease model is recapitulating the pathophysiology of the disease from its origin until its manifestation and progression. Each model is based on a slightly different pathogenic mechanism, and each has its strong points/similarities to psoriasis, as well as its limitations, not the least of which are the fundamental morphologic differences between human psoriatic skin and murine psoriasis models. As on today, a relatively large number of models have been developed to study the disease, each trying to mirror the complexity of the mechanisms. The objective of the current review article is to consolidate all the relevant literature pertaining to the various screening methods that have been employed to study psoriasis and psoriatic arthritis. This review has shortlisted the ex-vivo, in-vivo and in-vitro animal models for psoriasis which have been developed till date. Murine models in use employ xenotransplantation, direct induction method or knock-in and knock-out studies whereas models currently in use, in-vitro are 2-D and 3-D cell cultures. Also, the various therapies in existence to combat the disease have been highlighted. Although findings have been impressive, there still remains scope for identifying the ideal model of psoriasis which can mimic all the features of the disease.

KEYWORDS: Screening methods; psoriasis; xenotransplantation; phototherapy; biologics.

1. INTRODUCTION

Drug screening primarily aims to achieve two events, i.e. scanning and evaluation of the drug for detection of a physiological activity or pharmacological effect. This suggests that a particular substance must be worthy of attention only if it possesses interesting pharmacological properties. In this regard, it is imperative to design a test or series of experiments with skilful execution which are comprehensive, inexpensive and allow for distinguishing a useful drug from a non-useful drug.

For designing an ideal animal model for screening, the scientific observation must be qualitative as well as quantitative. Although there is prejudice against subjective methods, it is equally important to report those observations along with objective methods which are reliable and reproducible.

Psoriasis plaques is an autoimmune, chronic inflammatory skin condition that affects multiple organ systems and therefore mimicking this disease in animal models means justifying the 03 criteria for model validations, predictive, face and constructive validity; as identified by Willner (1984)[1] Further, these 3 criteria can be crucial for preclinical assessment of the drugs. A multifactorial approach can be adopted to recapitulate and extend the screening of drugs to a human setting since multidimensional procedures permit the investigator to obtain a wide range of data from each animal simultaneously and in an integrated form.

From such data the dose-response relations for different drug actions can be more meaningfully compared, and then be extrapolated to their appearance in man.[2]

Also, a quantal (all-or-none) approach in measurement, although easy can be misleading in cases where observations are difficult to quantify reliably, such as ataxia or muscle weakness or the degree of lesions. Therefore, a systematic, well-researched study presenting the etiology, symptoms, and pathogenesis of the disease

and the corresponding effect of different therapeutic regimens in a graded fashion rather than all-or-none, must be sought.

The current review focuses on highlighting the various screening methods that are currently in use and have been employed to study psoriasis plaques. Moreover, the different treatments for psoriasis which are safe and effective have been documented since the severity of disease dictates the need for alternative options. Further, the role of the immune system and the effect of genetics in relation to the disease have been mentioned. Lastly, comparison between existing models and a suggestion for future approaches have been summarised.

1.1 Findings regarding psoriasis and skin inflammation

Psoriasis is a chronic inflammatory skin disease with a strong genetic predisposition and autoimmune pathogenic traits. The worldwide prevalence is about 2%, but varies according to regions.[3] It shows a lower prevalence in Asian and some African populations, and up to 11% in Caucasian and Scandinavian populations.[4,5,6,7]

Psoriasis or plaque-type psoriasis is the more commonly known name for psoriasis vulgaris and has been used interchangeably in the scientific community. It manifests in different ways dermatologically and it's worthy to note that it presents distinct variations within its clinical subtypes.

Psoriasis is an autoimmune condition stemming from inappropriate activation of cutaneous T cells and dendritic cells, with subsequent release of inflammatory cytokines such as interleukin 1 (IL-1), IL-6, IL-12, IL-17, IL-23, and tumour necrosis factor (TNF)-α. These chemical signals are responsible for keratinocyte hyperproliferation manifesting as characteristic scaly plaques, and they also contribute to the rampant inflammation underlying a number of systemic disease associations, including metabolic syndrome, heart disease, and arthritis.[8]

To compete with this disease, several topical as well as systemic drug formulations have been identified, manufactured and utilised with varying degree of success.

Further, many studies have reported various factors contributing to the pathogenesis of psoriasis, including genetic factors, the immune system, and environmental conditions, thus recognizing it as a multifactorial disease.[9,10]

There are five types of Psoriasis: plaque, guttate, inverse, pustular, and erythrodermic. The most common form, plaque Psoriasis, typically has raised red or white scaly skin lesions with a thickened acanthotic epidermis.

Key findings in the affected skin of patients with Psoriasis include vascular engorgement due to superficial blood vessel dilation and altered epidermal cell cycle. Such changes are thought to be related to the various inflammatory cytokines released in the inflammatory process, such as TNF-α, interferon-γ (IFN-γ), and IL-17. Altered differentiation of psoriatic keratinocytes is characterized by an upregulation of the early differentiation markers (involucrin, small proline-rich proteins, keratin 6, keratin 16, and keratin 17), and downregulation of the late keratinocyte differentiation markers (filaggrin, loricrin, and caspase-14). Moreover, within the last decade, substantial advances have been made in elucidating the molecular pathogenesis of Ps.[11-17]

It has been observed that between 6 and 42% of patients with psoriasis develop psoriatic arthritis, which is characterized by stiffness, pain, swelling and tenderness of the joints. Nail psoriasis is highly prevalent in both plaque-type psoriasis and psoriatic arthritis and is found in approximately 50% of patients with psoriasis and in 80% of patients with psoriatic arthritis.[18] Apart from the genetic predisposition, there are several risk factors that trigger psoriasis which include trauma, infection, drugs, metabolic factors, stress, alcohol, smoking, and sunlight. Moreover, certain drugs that can exacerbate psoriasis include antimalarials, beta-blockers, bupropion, calcium channel blockers, captopril, fluoxetine, glyburide, granulocyte colony-stimulating factor, interferon, interleukins, lipid-lowering drugs, lithium, penicillin, and terbinafine.[19]

1.2 Screening methods known till date: the undemanding view

Amongst the known methods for screening of drugs for plaque psoriasis, the most widely used and recognised animal model of psoriasis was first published in 2009, the imiquimod-induced acute skin inflammation.[20]

In this model, 62.5 mg Aldara (5% imiquimod) is smeared onto the shaved dorsal skin of mice for 5 or 6 days to induce scaly skin lesions resembling plaque type psoriasis. While the model does not exactly recapitulate human psoriasis,[21] imiquimod treatment of mouse skin can exert specific cytokine expression patterns, histopathological alterations and cellular infiltrates similar to what is observed in psoriatic patients.[22]

Imiquimod is able to activate proinflammatory signalling pathways via the ligation of TLR7/8 upon dermal dendritic cells (DDCs), however, it is likely that other mechanisms such as NLRP1 inflammasome activation (pyroptosis)[23] direct activation of TRPA1 non-selective cation channels located on immune cells and peripheral nerve endings,[24] also contributes to its proinflammatory effects. While it is generally accepted that IL-17 producing Th17 cells are the main cell type responsible for the development of the skin inflammation, other

cells, such as subsets of the γδT17 cells also contribute to the immune reaction.[25]

Aldara-induced skin inflammation has several advantages compared to previous models of psoriasis, including rapid and reproducible skin response. Animals do not need pathogen free conditions, as seen in xenotransplantation models, and it is relatively inexpensive.[26] Consequently, this model also possesses several limitations. The overuse of the Aldara cream and its ingestion is the most problematic since it can cause severe systemic inflammation indicated by splenomegaly, worsened general condition and untimely death of the animals.[27] as it also affects the gut microbiome. This can contribute to the phenotypic variability observed in this model and it may likely be the reason for the different treatment regimens applied by various authors.[28-30]

In order to reduce the possibility of ingestion and direct scratching of the treated dorsal skin, Horvath et al., showed a new method for the induction of psoriasiform dermatitis in mice using Finn chambers. This new technique proved to be sufficient to elicit skin reactions such as edema, infiltration, scaling, increased blood perfusion, and psoriasiform histopathological alterations, similar to the classical imiquimod model. Moreover, it significantly reduced the other adverse effects of the imiquimod model by employing the same animals for psoriasiform affected and control group. This method can therefore be used for prolonged imiquimod treatments more accurately mimicking the chronic nature of psoriasis.[20]

Now, with the advances in genetic engineering, some transgenic animals and animals with targeted mutations (knockout and knock-in) have been developed to study psoriasis. In the case of knockout models, the targeted gene is inactivated and the phenotype is caused by the absence of the targeted gene product. In the case of knock-in model, the gene is modified through targeted point mutation, with the addition or deletion of a nucleotide, instead of complete disruption of the target gene expression, and the phenotype depends on the expression of modified gene products.[31]

Spontaneous mutation mouse models, such as homozygous asebia (Scd1ab/Scd1ab) mutant mice.[31] Flaky skin mice (Ttcfsn/Ttcfsn)[32] spontaneous chronic proliferative dermatitis mutation mice[33] and so on; do not closely mimic the disease enough to be considered as good models of psoriasis. They must rather be used to compare local pathogenic events such as hyperkeratosis, regulation of neutrophil infiltration and micro-abscess formation, or dermal angiogenesis.[31] But it is interesting to note that nearly a hundred mouse mutations that lead to psoriasiform phenotypes have been documented over the years.

Genetically engineered mice represent the largest category of psoriasis models. These include the transgenic and knockout models, such as human leukocyte antigen B27 (HLAB27) transgenic rats,[34] CD18 hypomorphic mice,[35] K14/VEGF and Tie2 mice,[36,37] K14/TGF-α, K5/TGF-β1, K14/KGF and K14/IL-20 transgenic mice,[38-40] IKK2.[41] and JunB/c-Jun transgenic mice,[42] K5.Stat3C mice,[43] and K14/IL-6 and K14/IL-1α transgenic mice.[44]

Although, so many transgenic approaches are available, the opposite strategy, i.e. deletion (or diminution) of putative key molecules, was also followed to study leukocyte b2 integrins (CD18) (in a hypomorphic mutation in PL ⁄ J mice)[35] IL-1ra,[45] (IRF-2)[46] or integrin aE.[47]

In addition, the role of signal transduction in psoriasiform skin inflammation was studied by deleting the inhibitor of nuclear factor (NF)-jB-kinase 2 (IKK2),[41] signal transducer and activator of transcription 3 (Stat3),[48] or Jun proteins,[42] within the epidermis. Another approach was by a group of scientists led by Hansson et al.[49] who developed a transgenic mouse strain that overexpresses the chymotryptic enzyme, which is also overexpressed in the stratum corneum of psoriatic skin. Pathological characteristics of psoriasis can be observed in this model.

To summarise, there are probably multiple reasons why an effective model mimicking all the features of psoriasis prove difficult and also why established therapies haven't proved exclusively effective. Although psoriasis appears as a disease of the skin, due to lesions observed, but the underlying alterations are many and go down till the cellular and molecular level. Metabolic and inflammatory disorders, biochemical interactions and genetic markers are the possible systems affected. Also, the genetically engineered animals or knock-in/knock-out models give rise to altered phenotypes and may lead to pathogenic components in the individual species.

Hence it can be said that there is no known naturally occurring disorder in non-human species that exhibits all of the pathologic alterations seen in psoriasis (i.e. chronic inflammatory erythrosquamous skin lesions under lied by epidermal hyperproliferation, altered differentiation, angiogenesis and a psoriasis-like infiltrate) and which responds to anti-psoriatic therapy.[31]

1.3 Approaches to attenuates the disease: unified way of drugs and formulations used

Plaque psoriasis is an unpredictable disorder with no absolute cure. In many cases it may not be life-threatening but can adversely affect the quality of life. Since it is a condition which predominantly showcases as lesions on the skin, it does not present an aesthetic appeal and thereby can lead to social isolation, lack of confidence, low self-esteem and depression among

patients. Any therapeutic strategy must keep in mind the age of the patient, quality of life and Psoriasis Area and Severity Index (PASI) score. This quantitative score measures the severity of psoriatic lesions based on area coverage and plaque appearance. It is a more specific technique since it not only takes into account the total body surface area (BSA), but also measures the intensity of redness, scaling and plaque thickness, ultimately producing a score from 0 (no disease) to 72 (maximal disease severity).

While systemic and biologic treatments are heavily relied on for severe and widespread skin disease, these medications do come with risks of systemic side effects and immunosuppression that many patients may not be willing or able to assume.

Broadly, treatment can be categorized as topical applications, phototherapy, systemic drugs and other modalities.

Topical therapy includes the use of emollients and moisturizers, corticosteroids, keratolytics, tar, anthralin, vitamin D3 analogs and calcineurin inhibitors. A combination of topical agents is sometimes more effective than when the drugs are used alone.[50-52]

Further, it has long been known that phototherapy is used to treat skin infections; specifically, ultraviolet radiation (UVA or UVB) in conjunction with coal tar, psoralen or anthralin paste. With advent in research, it has been identified as one of the most common treatment options for psoriasis. Research over the years has shortlisted predominantly four categories of action to describe the effects of phototherapy. These were alteration of cytokine profile, induction of apoptosis, promotion of immunosuppression and other mechanisms.

1.3.1 Alteration of cytokine profile – Psoriasis is thought to be a Th1/Th17 mediated inflammatory process driven by over-expression of Th1 and Th17-associated cytokines – leading to keratinocyte hyperproliferation and inflammation. In addition to this, a relative decrease in Th2 cytokines compared to normal skin has also been observed. These alternative patterns of cytokine expression are due to a host immune response that is guided by helper T cells. Several studies showed significant increases in IL-10 concentration i.e. its enhanced transcription and expression in UVB irradiated skin of healthy patients. Further investigation also described how phototherapy reverses the cytokine profile typically seen in psoriasis, by shifting the immune response towards the counter-regulatory Th2 axis and away from the Th1/Th17 inflammatory axis. Further, chronic plaque-type psoriasis lesions that were responsive to nbUVB treatment showed decreased expression of IFN-γ inducers in the Th1/Th17 pathways, specifically IL-12, IL-18, and IL-23.[53]

Moreover, researchers also found decreased expression of Th1/Th17 inflammatory cytokines, specifically IFN-γ, IL-12, and IL-23, in both the epidermis and dermis in the psoriatic lesions of fifteen patients who underwent twenty sessions of PUVA therapy.[54]

Another study found a decreased number of regulatory CD4+CD25+ T cells, as well as lowered levels of TNF-α in the serum of 12 patients with severe psoriasis after one-month of PUVA therapy—compared to before treatment.[55]

Hence it can be sufficiently stated that the effect of phototherapy in treating the condition of psoriasis may be due to an alteration in the cytokine profile.

1.3.2 Induction of apoptosis – Several studies have implicated apoptosis as a key process by which phototherapy is effective in the treatment of psoriasis. UVB-mediated apoptosis in human epithelial cells is thought to occur through DNA damage—particularly through the formation of pyrimidine dimers, and through injury to the cellular membrane—resulting in death receptor activation and the triggering of the apoptosis cascade.[56]

More specifically, UV light is thought to induce clustering and internalization of TNF, IL-1, and EGF receptors on cell surfaces,[57] and activate CD95 surface molecules,[58] both of which trigger pathways that lead to programmed cell death.

UV radiation is also believed to induce apoptosis by creating reactive oxygen species that damage cellular, mitochondrial, and nuclear membranes—and by directly damaging DNA.[59-61] Furthermore, UVB-irradiation can induce apoptosis of intraepidermal T cells, by increasing Fas-ligand expression on the surface of keratinocytes, which then bind to infiltrated T cells in the epidermis to trigger apoptosis.[62,63]

1.3.3 Promotion of immunosuppression – UV-induced immunosuppression has also been observed in several studies along with its effect on inducing apoptosis and altering the cytokine profile or inflammatory responses.

Researchers found a decrease in Langerhans Cells (LC) in non-lesional epidermal tissue in five psoriasis patients who were exposed to NB-UVB.[64] Similarly, decreased LC density was observed in healthy human skin after exposure to either UV solar simulated radiation, UVA radiation alone, or UVA + UVB.[65]

Further, decreased density of LCs in lesional epidermis was also observed in response to natural sun exposure.[66] Interestingly, researchers found significant reductions in LCs in the epidermis, and significant increases in LCs in the draining lymph nodes, in mice irradiated with chronic solar simulated radiation confirming the previous findings.[67]

Also, in vitro studies demonstrated that low-dose UVB irradiation of healthy human skin resulted in decreased dendritic cell expression of B7 co-stimulatory signals, which normally bind to CD28 and CTLA-4 on T lymphocytes.[68]

Other immunomodulatory effects of phototherapy were demonstrated when a team of Japanese researchers discovered evidence of decreased mast cell degranulation and histamine release from UVB and PUVA irradiated skin in animal models.[69-71]

These findings that may be associated with the reduction of erythema and pruritus in psoriatic lesions.[72]

1.4 The insight on other mechanisms involved

The other mechanisms proposed to describe the therapeutic action of phototherapy in psoriasis are the inhibition of dsRNA activity, altering the gene expression and arresting the cell-cycle.

Therefore, phototherapy serves as a reasonable and effective treatment option for patients requiring more than topical medications and/or those wishing to avoid systemic medications or simply seeking an adjunct to a failing regimen. Although, in these processes or mechanisms of action, which occurs first still remains unclear and whether, other modalities are working in unison to give the therapeutic effects of this treatment or precisely how these mechanisms are interrelated can be the scope for future studies.

Common sources of light therapy used in the management of plaque psoriasis include whole-body or targeted ultraviolet (UV) B (broad and narrow band), photochemotherapy (psoralen with UVA (PUVA)), home phototherapy and LASER among which narrow band UVB and psoralen UVA are particularly effective.

1.4.1 NB UVB – Narrow band UVB which is in the range of 311 – 313 nm has effectively been used for the treatment of generalised plaque psoriasis. The dosage depends upon the minimal erythema dose (MED) and type of skin. Upon observations by researchers, a frequency of twice – thrice weekly is recommended. More specifically, patients receiving twice weekly NB-UVB treatments achieve clearance in a mean of 88 days compared with 58 days for those receiving 3 treatments per week.[73] Further, application of a thin layer of emollient, such as petrolatum, is recommended before NB-UVB treatment sessions, as this increases treatment effectiveness in psoriasis and also reduces UV-induced erythema.[74-76]

In addition to this, NB-UVB treatment was compared with PUVA in studies performed by other researchers. Though the end result was ultimately the same, PUVA resulted in faster clearance with less treatment than with NB-UVB (12.7 treatments, and 49.2 days for PUVA compared with 16.4 treatments and 65.6 days for NB-UVB). Also, in a retrospective cohort study of 293 patients with psoriasis treated with various types of phototherapy at a single center, 55 of 69 patients treated with NB-UVB (79.7%) achieved a good (60%-80% skin clearance) or excellent (80%-100% skin clearance) response.[77] It was observed that although more effective, oral PUVA causes a higher rate of adverse effects, with symptomatic erythema and blistering observed in 17% of patients versus in 7.8% with NB-UVB.[78]

These findings suggest that NB-UVB is a potential treatment options for ameliorating the symptoms of plaque psoriasis.

As mentioned previously, among the systemic drug formulations used, the options available are acitretin, methotrexate, cyclosporine, tacrolimus, hydroxyurea, 6-thioguanine, mycophenolate, fumaric acid esters, apremilast and biologic agents.[8]

Years of research have identified that the goal of therapy in treating psoriasis is not only to reduce skin and joint symptoms and prevent further structural damage in those with Psoriatic arthritis (PsA), but also to make a meaningful impact on health-related quality of life (QOL). Ultimately, care of patients with psoriasis or PsA must be individualized, taking into account efficacy, adverse effects, availability, ease of administration, and cost of therapy, as well as patient comorbidities and illnesses.[8]

One of the prominent drugs highlighted in the recent years was apremilast (Otezla, Celgene corporation). It is a drug approved by the FDA in 2014, as the first selective phosphodiesterase PDE-4 inhibitor indicated for adults with active psoriatic arthritis. Although the exact mechanism by which it exerts its effect is not known, many of the cytokine mediators involved in the disease are influenced by PDE-4 and thereby instrumental in altering the inflammatory processes.[79]

By inhibiting PDE4, apremilast prevents the degradation of cyclic adenosine monophosphate (cAMP). The subsequent increased level of cAMP results in an antagonistic effect on the production of proinflammatory cytokines such as TNF-α, IL-23, and interferon (IFN)-γ, and an increase in anti-inflammatory mediators (e.g., IL-10).[80] Thus, apremilast works intracellularly to interrupt the inflammatory cascade at an early point, unlike biologic agents that target single pro-inflammatory markers (e.g., TNF-α). In healthy subjects, the plasma clearance of apremilast is approximately 10 L/hr and the terminal elimination half-life ranges from six to nine hours.[81,82]

Several clinical studies were also carried out to identify characteristics of the drug and evaluate safety and efficacy of apremilast in patients with psoriasis or psoriatic arthritis. One of the studies pointed out the adverse events which were largely mild to moderate in

severity and dose-dependent. These included diarrhea, reported by 11% and 19% of patients in the apremilast 20-mg and 30-mg groups, respectively (versus 2% for placebo), and nausea, reported by 10% of apremilast 20-mg patients and 19% of apremilast 30-mg patients (versus 7% for placebo)[79] Apart from these mild side effects, the overall baseline characteristics and background disease characteristics were nearly the same across different clinical studies. Further, it was observed that methotrexate, which is a known drug for treating psoriatic arthritis, showed no drug interactions with apremilast, whereas, rifampin proved to be a strong inducer for CYP3A4. Also, the recommended maintenance dose of apremilast, irrespective of indication, is 30 mg twice daily administered without regard to meals. Therefore, it can be said that apremilast has provided clinicians with a new tool in their arsenal for compating against psoriatic arthritis.

Of the available biologic agents, etanercept, adalimumab, infliximab, secukinumab, ustekinumab, tildrakizumab and ixekizumab are indicated for plaque psoriasis among others which have been briefly enlisted below.

Etanercept can be safely used in children with proper monitoring. Other treatment modalities like fish oil rich in omega-3 fatty acids may be of benefit.[83] Certain examples of the various biological formulations are mentioned below.

Infliximab is a chimeric human-murine monoclonal antibody directed against tumour necrosis factor α. It has been approved in the USA and EU for the treatment of plaque psoriasis and psoriatic arthritis at a recommended dosage of 5 mg/kg administered by intravenous infusion at 0, 2 and 6 weeks, then every 8 weeks thereafter.[18]

Brodalumab is a human monoclonal IgG2 antibody that selectively binds to human IL-17RA and inhibits its interactions with cytokines IL-17A, IL-17F, IL-17C, IL-17A/F heterodimer and IL-25. IL-17RA is a protein expressed on the cell surface and is a required component of receptor complexes utilized by multiple IL-17 family cytokines. Blocking IL 17RA inhibits IL-17 cytokine-induced responses including the release of pro-inflammatory cytokines and chemokines. SILIQ (brodalumab) injection for subcutaneous use is a human interleukin-17 receptor A (IL-17RA) antagonist indicated for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy and have failed to respond or have lost response to other systemic therapies.[84] It is contraindicated in Crohn's disease and shows adverse reactions like infections of the upper respiratory tract, latent tuberculosis or nasopharyngitis, and suicidal ideation and behaviours.[84]

Further, a group of scientists led by Krueger, tested an antibody directed against IL-15 that was known to inhibit the production of T lymphocytes as well as the liberation of TNF-α in vitro.[85] Application of this antibody in severe combined immunodeficient mice (SCID) led to the disappearance of psoriatic characteristics.

Neuropeptide-modulating agents, newer NSAIDs like WBI-1001, LAS41002, and LAS41004, Janus-associated kinase inhibitors, MEK1/MEKK1 inhibitor, phosphodiesterase inhibitors, pan-selectin antagonists, and fibroblast growth factor 23 (FGF 23), are under research. The role of alefacept in HIV-associated psoriasis is also being considered.[86]

Table 1: The table enlists the drugs (synthetic, biologics) which have been used for the treatment of psoriasis or psoriatic arthritis.[88]

Sr. no.	Drug	Mechanism	Appli-cation
1.	Methotrexate	Dihydrofolate reductase inhibition blocks purine biosynthesis; induction of lymphocyte apoptosis	s.c./oral
2.	Cyclosporin	Calcineurin inhibition leading to reduced IL-2	Oral
3.	Acitretin	Normalization of keratinocyte proliferation/differentiation through retinoid receptor binding	Oral
4.	Fumarate	Intracellular glutathione, modulation of Nrf2, NF-κB, and HIF-1α; promoting a shift from a pro-inflammatory Th1/Th17 response to an anti-inflammatory/regulatory Th2 response.	Oral
5.	Apremilast	PDE4 inhibitor increases intracellular cAMP levels in immune and non-immune cell types modulating inflammation	Oral
6.	Etanercept (Enbrel) Contraindicated in MS, weak immune system, Hepatitis B, Heart failure Etanercept-szzs (Erelzi)	Dimeric human fusion protein mimicking TNF-αR, Biosimilars	s.c.
7.	Infliximab (Remicade)	Chimeric IgG1κ monoclonal antibody that binds to soluble	i.v.

	Infliximab -dyyb (Inflectra) Infliximab -abda (Renflexis)	and transmembrane forms of TNF-α Biosimilars	
8.	Adalimumab (Humira) Adalimumab-atto (Amjevita) Adalimumab-adbm (Cyltezo)	Human monoclonal antibody against TNF-α Biosimilars	s.c.
9.	Certolizumab pegol (Cimzia) Contraindicated in MS, Crohn's disease, ulcerative colitis	Fab portion of humanized monoclonal antibody against TNF-α conjugated topolyethylene glycol	s.c.
10.	Ustekinumab (Stelara) A rare condition called reversible posterior leukoencephalopathy may occur	Human IgG1k monoclonal antibody that binds with specificity to the p40 proteinsubunit used by both the interleukin (IL)-12 and IL-23 cytokines IL-12/IL-23 p40	s.c.
11.	Tildrakizumab-asmn (Ilumya)	Humanized IgG1κ, which selectively blocks IL-23 by binding to its p19 subunit	s.c.
12.	Risankizumab-rzaa (SKYRIZI) (approved in 2019)	Humanized IgG1 monoclonal antibody that inhibits interleukin-23 by specificallytargeting the p19 subunit	s.c.
13.	Guselkumab (Tremfya)	Human immunoglobulin G1 lambda (IgG1λ) monoclonal antibody that selectively blocks IL-23 by binding to its p19 subunit	s.c.
14.	Secukinumab (Cosentyx)	Human IgG1κ monoclonal antibody against IL-17A	s.c.
15.	Ixekizumab (Taltz)	Humanized, immunoglobulin G4κ monoclonal antibody selectively binds and neutralizes IL-17A	s.c.
16.	Brodalumab (Siliq)	Human monoclonal IgG2 antibody directed at the IL-17RA	s.c.
17.	Abatacept (Orencia)	Selective T cell co-stimulation modulator, used for juvenile idiopathic arthritis	i.v., s.c.
18.	Golimumab (Simponi)	TNF-a blocker, used in combination with methotrexate	s.c.

Biologics or complex engineered molecules primarily act by two pathways: the IL-23/Th17 axis and TNF-α-signalling. Although, biologics have several advantages over other synthetic formulations, they also possess severe adverse effects and can lead to many inflammatory diseases or some type of cancers. In lieu of this, considering biosimilars for use against psoriasis and psoriatic arthritis is a viable option. Biosimilars are approved drugs as they are "highly similar agents" with a drastically reduced cost. For a biosimilar drug to receive FDA approval, it must be highly similar to the original biological drug and contain no clinically meaningful differences, although there may be minor differences in clinically inactive ingredients. According to the National Cancer Institute, the biosimilar also must prove to be "as safe as, work as well as, and work in the same way as" the original drug, and "be used in the same way, at the same dose, and for the same condition."

While devising treatments, extra care must be taken while treating a pregnant woman with psoriasis. In the case of phototherapy, UVB can be safely used, and the risk of topical PUVA is considered low in pregnancy. According to the US FDA, adalimumab, etanercept, and infliximab come under FDA category B; anthralin, betamethasone dipropionate, calcineurin inhibitors, cyclosporine, psoralen, methylprednisolone aceponate are category C drugs; whereas, acitretin, methotrexate, and tazarotene belong to category X.[87]

The choice of therapy should take into consideration the long-term side effects of therapy with particular reference to topical steroids and other immune-suppressive agents. High-potency topical steroids like clobetasol propionate are contraindicated in young children for fear of side effects like atrophy, depigmentation, and precipitation of pustular psoriasis on sudden withdrawal (which may also occur in adults using excessive quantities over a long period). While using phototherapy and systemic drugs, a similar caution should be exercised. In children, immature hepatic andrenal systems, and the active hematopoietic system should be carefully considered when prescribing systemic drugs. Since the long-term side effects of newer drugs are not yet available, it is prudent to use them only when indicated and other treatments have failed or are contraindicated.[87]

In summary, topical therapy and phototherapy are used in mild-to-moderate psoriasis, and systemic therapy is indicated for more severe disease. Biologics should be instituted by qualified experts only when indicated.[87] Certain drugs in the research pipeline that may be utilised for psoriasis are Tofacitinib, an oral Janus kinase

(JAK) inhibitor currently approved for the treatment of rheumatoid arthritis (RA) and PsA. Tofacitinib showed a 59% PASI 75 and 39% PASI 90 response rate at week 16, and was also effective for nail psoriasis; however, its development for psoriasis was halted for reasons unrelated to safety. Next, Upadacitinib, another JAK inhibitor currently is undergoing phase III clinical trials for the treatment of psoriatic arthritis. Piclidenoson, an adenosine A3 receptor inhibitor, serlopitant, a neurokinin-1 receptor antagonist, and RORγt inhibitors are each being tested as oral treatments for psoriasis.[88]

Overcoming the potential side effects of existing drugs and providing an improved effective treatment plan for billions of people worldwide, traditional systems of medicine in Thailand have utilised many different plants for the treatment of dermatological conditions. Although, the scientific community is skeptical due to lack of preclinical or clinical evidence, these traditional systems have proven to be effective. Wannachawee Recipe (WCR) has been enlisted in the Hospital Traditional Medicine Formulary and has been used as a Thai medicine for the treatment of psoriasis in the Thai Traditional Medicine Clinic of Prapokklao Hospital since 2006.[89]

A previous study by Na Takuathung et al. has demonstrated that WCR can inhibit the growth and viability of keratinocytes. In addition, WCR significantly decreases the gene expression of IL-1β, IL-6, IL-8, IL-17A, IL-22, IL-23, and TNF-α as well assignificantly decreasing the secretion of IL-17A, IL-22, and IL-23 in TNF-α- and IFN-γ-induced HaCaT cells.[90] Therefore, clinically it has been found to possess potent anti-inflammatory activity. WCR also significantly reduced the spleen weight to body weight ratio along with a decrease in the cellularity of the periarteriolar lymphoid sheaths (PALS, T-cell area).[89]

Another example is delivery of tacrolimus (TAC), a macrolide immunosuppressive inhibitor of calcineurin, that attacks on some cytokines involved in pathogenesis of disease. A multifunctional nanostructure lipid carrier (NLC) was developed to co-delivery TAC and siRNA. The release study demonstrated a controlled release of TAC, and the permeation and retention profile in the skin tissue show to be promising for topical application.[90]

The developed system was successfully used to treat in vivo psoriatic animal model induced by imiquimod and the synergic combination between TAC and siRNA was reported for the first time.[90]

The macroscopic and histological images corroborate the intuition that the multifunctional treatment provided the group animals with a treatment where their appearance and TNF-α dosage were similar to that of healthy animals.[90]

Although many potential new molecules are being discovered, designed and developed, the need for preclinical and clinical studies for investigating toxicities of the drugs cannot be understated.

1.5 Existing drawbacks in model development

Animal models are very popular for the study of psoriasis. Many approaches are currently followed in order to obtain a representative animal model of the disease with all the characteristics of the human pathology. Many immunological and genetic models have also been developed to date.[92] Every model for drug screening has certain drawbacks and areas of concern which are met by another newer well-researched technique. A general comparison between the in-vitro and in-vivo models for studying the physiological or pharmacological effect of drugs on psoriasis plaques is explained as follows.[93]

1.5.1 Comparison between in-vitro and in-vivo animal models: The Possible significant outcome

Although in-vitro models are easily accessible and can be studied, utilise the human tissues (xenotransplantation) thereby not utilising animal models, and allow responses of individual cells to be assessed, they pose challenges in comparison to in-vivo models because they discount the influence of macro- and microenvironment sources. Further, in-vivo models are tricky to study since they involve multiple signalling pathways and depending upon the type of research present varied modifications. In-vivo models present certain disadvantages too. Responses can be affected because of the environment, by making a single gene manipulation the entire reconstruction of the disease can not be possible. Also, the human and animal skins degree of immunity may vary.[94]

Among its utility, in-vitro models can be employed to study phenotype, function and responses to stimulators and inhibitors, and evaluate the viability and physiology of the cell. Whereas, in-vivo models are suitable for researching the multifarious interactions between skin cells, vascular endothelium and immune response.[94]

1.5.2 Comparison between human and skin models: Next footstep

Even though mice are commonly used as skin disease models, there are inherent differences in skin structure between mice and human skin. Mouse skin is significantly thinner, and global nucleotide excision repair (NER), the most important DNA repair mechanism acting in humans, appears less relevant in mouse skin.[95] In human skin, melanocytes are located in the basal layer of the epidermis, where they make dendritic connections with the surrounding keratinocytes.[96,97] Melanosomes are transferred from melanocyte to keratinocytes, providing skin pigmentation and also protection from ultraviolet radiation (UVR).[96] However, in mouse skin, melanocytes arelocated mainly at the base of the hair

follicles embedded in the dermis and are only found in the epidermis of the hairless areas, that is ears, tail, and paws,[9] or at dermal – epidermal junction at specific periods (e.g., during embryogenesis or postnatal).[98] Discrepancies exist in both innate and adaptive immunity, including balance of leukocyte subsets, defensins, Toll receptors, inducible NO synthase, cytokines and cytokine receptors, Th1/Th2 differentiation, Ag-presenting function of endothelial cells, and chemokine and chemokine receptor expression.[99] Moreover, there are also differences in the cell signaling and functional profiles of oncogenes and tumor suppressor genes between mice and humans.[100]

1.6 Genetic and non-genetic inheritance of Psoriasis

Psoriasis has a genetic component that is supported by patterns of familial aggregation. It is interesting to note, that although it is a chronic inflammatory skin disease it does have a genetic component.

First and second-degree relatives of psoriasis patients have an increased incidence of developing psoriasis, while monozygotic twins have a two to three-fold increased risk compared to dizygotic twins.[101,102] Determining the precise effect of genetics in shaping innate and adaptive immune responses has proven problematic for psoriasis and other numerous immune-mediated diseases.[103,104] The genetic variants associated with psoriasis are involved in different biological processes, including immune functions such as antigen presentation, inflammation, and keratinocyte biology.[105]

The most prominent locus linked to psoriatic susceptibility is PSORS1, among the 60 chromosomal loci so far identified. PSORS1 is located onchromosome 6p21 within the major histocompatibility complex (MHC), which is specifically in theclass I telomeric region of HLA-B, and spans an approximately 220 kb-long segment and correspondsto HLA-Cw6 (C*06:02).[106]

HLA-Cw6 is strongly linked to early and acute onset psoriasis [90,91]. The HLA-C*06:02 allele is present in more than 60% of patients, and increases the risk for psoriasis nineto 23-fold.[106]

1.7 Role of autoimmunity in psoriasis

Psoriasis shows clear autoimmune-related pathomechanisms. This very important area of research will allow for a deeper understanding of to which extent autoantigen-specific T cells contribute to the development, chronification, and overall course of the disease. LL37 is one of two well-studied T cell autoantigens in psoriasis. CD4+ and CD8+ T cells specific for LL37 were found in two-thirds of patients with moderate to severe plaque psoriasis in a study. LL37-specific T cells produce IFN-γ, and CD4+ T cells produce IL-17, IL-21, and IL-22 as well. LL37-specific T cells can be found in lesional skin or in the blood, where they correlate with disease activity.[107] CD8+ T cells activated through LL37 engage in epidermotropism, autoantigen recognition, and the further secretion of Th17 cytokines. The melanocytic protein ADAMTSL5 was found to bean HLA-C*06:02-restricted autoantigen recognized by an autoreactive CD8+ T cell TCR. This finding establishes melanocytes as autoimmune target cells, but does not exclude other cellular targets.[108] Other autoantigen candidates include lipid antigens generated by phospholipase A2 (PLA2) group IVD (PLA2G4D) and hair follicle-derived keratin 17.[109, 110] Interestingly, keratin 17 exposure only lead to CD8+ T cell proliferation in patients with the HLA-Cw*0602 allele.[111] These findings suggest the probable role of autoimmunity which must be considered while designing models for psoriasis.

1.8 Skin inflammation associated with psoriasis

Psoriasis is characterized by excessive, cytokine-driven epidermal hyperplasia.[112] Normal epidermis contains almost 10 cell layers made up of the basal layer, spinous layer, granular layer, and stratum corneum. Stratum corneum is constantly sloughed off andreplenished via proliferation in the basal layer. In psoriasis lesions, the granular layer isoften absent and corneocytes retain their nuclei.[93] Stratum corneum is thicker and disorganized. Lipids are not secreted in a normal fashion into the extracellular spacewhich leads to a defective water/vapor barrier and the shedding of stratum corneumfragments in large sheets so-called scales or flakes in psoriasis plaques.[93] Components of cornified envelope (CE) are prematurely synthesized in the spinous layer.[93] Connexin 26(Cx26) is a gap junction protein which is highly upregulated in psoriasis, and transgenic overexpression of Cx26 in mouse epidermis keeps wounded epidermis in a hyperproliferative state while blocking the transition to remodeling. In addition to this, its upregulation also leads to infiltration of immune cells.[93]

Also, it has been found that psoriatic lesions have heightened requirements for glucose uptake and metabolism as evidenced by increased Glut1 expression and PET scans.[113] Metabolomic studies have demonstrated increased levels of some amino acids in the serum patients with psoriasis.[114,115] Metabolomic analysis of the epidermis of Glut1 deficient mice revealed decreases in a similar set of amino acids. Therefore, inhibiting glucose transport could impact metabolic pathways critical to the development of psoriasis. Consistent with this prediction, Glut1 deficient mice were protected from imiquimod-induced psoriasiform hyperplasia.[116]

Further, the topical application of a Glut1 inhibitor was also effective in protecting mice from imiquimod-induced psoriasiform hyperplasia as the systemic inhibitor was predicted to cause neurologic sequelae, hyperglycemia, and lipodystrophy.[117]

Similar to the deletion of Glut1 in keratinocytes, chemical inhibition of Glut1 inhibited the epidermal proliferation and acanthosis. Topical transport inhibitors had the added feature of suppressing the inflammatory infiltrates and cytokine secretion in animal models of psoriasis and human psoriatic skin organoids, respectively. Consistent with previously reported roles for Glut1 and glucose metabolism in T lymphocyte activation,[118,119] it can be speculated that the topical application of WZB117 might also inhibit glucose uptake in other cell types in the skin, including infiltrating lymphocytes, and thereby limit inflammation in vivo.[116]

It can now be well established that psoriasis occurs when there is a disruption in the anti-inflammatory regulation of individuals in the immunological as well as non-immunological skin-resident cells.[116]

Moreover, Rodríguez-Martínez et al. (2017) very methodically represented an illustration that enabled an understanding of the process of inflammation; its mechanism as generated in the skin of healthy individuals, and compared it to the workings of a cogwheel.

In this, a trigger induces the innate and adaptive immune response, and in turn angiogenesis and keratinocytes proliferation are activated. Every cog represents one participant in inflammation: cell (DCs, macrophages, iLC IL-17+, Th1, Th17, keratinocytes, between others) or molecule (TLRs, NFκB, βTrCP, IκBζ,Stat3, TNFα, IFNα, IL-12, IL-36, IL-23, Th1, IL-6, Th17, IL-17, CCR6, VEGF, Tie2 TGFβ1,PPARαβ, PK2, between others). The movement of the cogwheels in a particular fashion leads to progression of inflammation. In healthy people, the inflammation is controlled by the activation of anti-inflammatory process after damage reparation. The cells (Treg andM2 macrophages) and molecules (IκBα, JunB, SOCS3, IFNR-2, IL-36RA, IL4, IL-10, IL-35, CD18, VHL, Tnip-1, between others) are also involved in the anti-inflammatory process. The cogwheels in the opposite fashion indicate the progression of anti-inflammation. Moreover, there are certain "ghost" cogs representing dysfunctional molecules or cells that disrupt effectiveness in the control of inflammation, favouring the development of psoriasis.[120] This model represents a clear map to allow for developing new strategies and creating novel models for disease.

1.9 Future prospects for model developments

So far, well established models for psoriasis include spontaneous mutations and genetically engineered models that have been discussed at length in this review. Now, with the advances in genetic engineering, some transgenic animals and animals with targeted mutations (knock-out and knock-in) have been developed to study psoriasis. In the case of knockout models, the targeted gene is inactivated and the phenotype is caused by the absence of the targeted gene product. In the case of knock-in model, the gene is modified through targeted point mutation, with the addition or deletion of a nucleotide, instead of complete disruption of the target gene expression, and the phenotype depends on the expression of modified gene products. Knockout and knock-in animals are also developed with the use of tissue specific promoters to eliminate or express the targeted gene, and even more, the expression or suppression of the gene could be controlled by specific promoter regulators, where antibiotics and hormones are frequently used.[121]

Another strategy that has been identified to study psoriasis and other dermatologic illnesses in vitro is the development of 2nd or 3rd-dimensional cell co-cultures. 2D model consists of primary explants of keratinocytes or fibroblasts from psoriatic patients cultured over extracellular matrix proteins toevaluate cellular proliferation, cellular differentiation and cytokines production.[122]

In the 2D – membrane model, two cell types are co-cultured separated by a synthetic membrane to evaluate the interconnection between two cell types in the pathology.[123] 3D cultures, also known as organotypic culture system (OCS), allow the growth of complex biological systems in vitro in a way that resembles part of their normal physiology and function. OCSs are powerful as experimental platforms in preclinical dermatological research, helping to validate mechanisms of diseases and to test the therapeutic potential of candidate drugs.[124] The new generation of 3D cultures connected to biosensors or chips allows real-time monitoring of biological parameters such as loss of water and electrophysiologic parameters.[125]

Further, imiquimod-induced murine psoriasis, one of the highly effective models, which resulted in an acute inflammation in the epidermis induced by imiquimod, hyperactivating the innate immunity and leading the adaptive immunity to produce great amounts of IL-17 has also been very popular among researchers.

In this model, IL-17, in turn, induces angiogenesis and proliferation of keratinocytes, as biological characteristics of psoriatic lesions. Apart from this, xenotransplantation or humanised animal models have also been created for the evaluation of anti-psoriatic treatments. They consist in the transplantation of human skin in the back of immunodeficient mice.[30] Xenotransplantation experiments have been performed in which a skin biopsy from a patient or a skin equivalent produced in vitro was transplanted on mice from spontaneously mutated or genetically modified strains. Over the years, many models for in-vivo studying have been identified and few of them are enlisted below.

1. Athymic nude mouse – in this athymic nude mice were mainly used to verify if there was a difference between involved and uninvolved psoriatic skin.[126,127] It was found that

involved psoriatic skin maintains its psoriasiform histology when transplanted onto nude athymic mice such as epidermal thickness and papillomatosis.[126] However, not all the characteristics of the pathology was preserved. In fact, psoriatic epidermis did not contain polymorphonuclear leucocytes after grafting on athymic nude mice. In a further study, uninvolved psoriaticepidermis from psoriatic patients seemed to be able to display markers of involved psoriaticepidermis independently from the psoriatic host.

2. Severe combined immunodeficient mice (SCID) – this is probably the most widely used relevant model for psoriasis, but the presence of NK which are involved in rejection of xenogeneic tissue is a severe inconvenience.[128] In fact, single-cell suspensions are rapidly recognized and lysed by mice NK cells.[129] However, in SCID mice, grafts of solid tissues are well tolerated and psoriatic characteristics are maintained for several months in the transplantations involving psoriatic skin.[130,131] Raychaudhuri et al., noticed that clinical, histological and immunological features of psoriasis could be maintained for durations of 12-16 weeks, while Sugai et al. conserved the human psoriatic skin transplant for up to 22 weeks.[132] Therefore, it was observed that the chances for transplant rejection were less in this case.
3. Spontaneous AGR129 model – Boyman et al. demonstrated that human uninvolved psoriatic skin grafted onto AGR129 mice spontaneously developed psoriatic plaques without injection of activated immune cells or any other exogenous factor. In fact, skin grafts developed a psoriatic phenotype in 28 of 31(90 %) grafted mice.[133] Histology of developed plaques was comparable to psoriatic lesion biopsies from the same patient. Boyman's team also noticed that when they injected an inhibitor of T cells (monoclonal anti-CD3), the psoriatic phenotype disappeared.
4. These were examples of the various models which were tried for psoriatic treatment in vivo. Further, in – vitro models possess certain features. (1) inflammatory cells can be included in most of the in vitro models, (2) these models allow to dissect step by step the mechanisms of psoriasis by isolating or combining the cell types and (3) recent studies using animal models, including the IKK2.[134] and JunB/c-Jun transgenic mice.[135] are challenging the immunological theory of psoriasis. They are of the following types: 1. Monolayer – IL -15, TGF-α regulates VEGF, S – phase; 2. De-epidermised dermis – organ culture, keratinocytes; 3. Collagen gel – organ culture, skin substitutes; self- assembly – skin substitutes.[136]

1.10 Conclusion: current best methods for screening

Very recently, the discovery of the clustered regularly interspaced palindromic repeats (i.e., CRISPR)-associated (Cas9) system in prokaryotes has transformed the laboratory science of genetic engineering. This gene editing technology is already being used in dermatology research,[137] and has been used to generate transgenic mice for preclinical psoriasis studies.[138] The primary advantages of this technology are the precision of its gene editing mechanisms, the ability to alter multiple genes simultaneously via a single guide RNA, and the decreased amount of time required to generate a transgenic mouse compared with traditional technologies. Its main limitations are its off-target biological effects and the observed variations in single guide RNA efficiency. Although CRISPR/Cas9 technology represents an exciting, powerful gene editing technology with enormous potential, its introduction into dermatology research is relatively new. Therefore, the implications of this technology are not fully understood but it can pose as a possibly new strategy for intervention in studying the physiology of disease.[139]

Lastly, the successful development of novel therapies requires a translational approach to develop and implement the best preclinical and experimental clinical models and analytical tools that capture the various biological aspects of the disease. There is a need for more advanced in vitro skin models that contain the relevant cellular constituents as well as a need for careful validation of relevant in vivo models for psoriasis. The use of xenotransplants have confirmed the important role of immunology in this disease. The studies done in genetically modified mice that overproduce (transgenic) or lack (knockout) certain proteins reveal specific protagonists of innate or adaptive immunity, angiogenesis or proliferation for the development of psoriasis Although these techniques have proven to be effective for understanding the pathophysiology, symptoms, and suggest possible therapeutic interventions for treatment of psoriasis and its allied effects; no animal model or system can effectively mimic all the features of the human physiology but can still allow a high degree of specificity that enables the researchers to come to probable solutions.

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