Review Article

Psoriasis: ATreatable but not so far Curable Disease

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Abstract

Research on psoriasis pathogenesis has largely increased knowledge on skin biology in general. In the past 15 years, innovations in the understanding of the pathogenesis of psoriasis have been translated into targeted and highly effective therapies providing fundamental insights into the pathogenesis of chronic inflammatory diseases with a dominant immune axis. This review we briefly discuss the pathophysiology of the disease, presence of comorbidities such as psoriasis arthritis and in detailed present the therapeutic options available now and in future for the this treatable disease. We present here a compiled data on well-established widely available therapies and novel targeted drugs.We aimed to focus on mechanism of action, doses, route of administration and established side effects. This information will be helpful for the clinicians to decide on the drugs for their patients.

Keywords: Psoriasis, Therapy, Small molecules, Biologics, Novel drugs.

Introduction

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[1]. It shows a lower prevalence in Asian and some African populations, and up to 11% in Caucasian and Scandinavian populations[2].The dermatologic manifestations of psoriasis are varied. This can be classified into Psoriasis Vulgaris, Inverse Psoriasis, Guttate Psoriasis and Pustular psoriasis[3].

Although, psoriasis is dermatological disease, it also affects the joints, inflammation mayaffect different organ systems and may associated with several diseases. It is considered that psoriasis has number of systemic complications. These patients may have hypertension, increased hyperlipidemia, coronary artery disease, increased body mass index and type 2 diabetes as compared to healthy patients[4]. Psoriasis also independently raises risk for myocardial infarction, stroke, and death due to cardiovascular disease[5]. It is suggested that low-grade inflammation, commonly observed in the psoriasis accelerate vascular disease development [6]. Major danger of chronic psoriatic inflammation is the development of psoriatic arthritis (PsA). The skin manifestations generally lead to PsA and requires systemic therapies due to a potential destructive progression. Psoriatic arthritis develops in up to 40% of psoriasis patients[7]. Psoriasis also linked with gastro-intestinal (Crohn's disease and inflammatory bowel disease), kidney disease, liver diseases[8]. Different factors contributing to psoriasis as a systemic disease can have a dramatic effect on the quality of life of patients and their burden of disease. Psoriasis impairment to psychological quality of life is comparable to cancer, myocardial infarction, and depression. The high burden of disease is thought to be owed to the symptoms of the disease, which include pain, pruritus, and bleeding[9].

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Pathogenesis

The characteristic of psoriasis is persistent inflammation that leads to uncontrolled keratinocyte proliferation and dysfunctional differentiation. The histology of the psoriatic plaque shows acanthosis (epidermal hyperplasia), which overlies inflammatory infiltrates composed of dermal dendritic cells, macrophages, T cells, and neutrophils. Disturbances in the innate and adaptive cutaneous immune responses are responsible for the development and sustainment of psoriatic inflammation[10]. Additionally, psoriasis shows traits of an autoimmune disease on an (auto) inflammatory background. The development of the psoriatic plaque is not restricted to inflammation in the epidermal layer. The pathogenesis of psoriasis can be conceptualized into an initiation phase possibly triggered by trauma (Koebner phenomenon), infection, or drugs and a maintenance phase characterized by a chronic clinical progression[11].

Therapeutic options for Psoriasis

Psoriasis is a chronic relapsing disease, which often necessitates a long-term therapy. The choice of therapy for psoriasis is determined by disease severity, comorbidities, and access to health care. Psoriatic patients are frequently categorized into two groups: mild or moderate to severe psoriasis, depending on the clinical severity of the lesions, the percentage of affected body surface area, and patient quality of life[12].Clinical disease severity and response to treatment can be graded through a number of different scores. The PASI score has been extensively used in clinics for the assessment of drug's efficacy. Mild to moderate psoriasis can be treated topically with a combination of glucocorticoids, vitamin D analogues, and phototherapy. Moderate to severe psoriasis often requires systemic treatment.

Tonsillectomy

A number of case reports and case series have suggested that tonsillectomy has a therapeutic effect in patients with guttate psoriasis and plaque psoriasis[13]. A systematic review concluded that the evidence is insufficient to make general therapeutic recommendations for tonsillectomy, except for selected patients with recalcitrant psoriasis, which is clearly associated to tonsillitis [13]. To date, a single randomized, controlled clinical trial showed

that tonsillectomy produced a significant improvement in patients with plaque psoriasis in a two-year follow-up timespan. Furthermore, the same cohort was evaluated to assess the impact of the clinical improvement after tonsillectomy on quality of life. The study reported a 50% improvement in health-related quality of life, and a mean 59% improvement in psoriasis-induced stress.

Tonsillectomy was considered worthwhile by 87% of patients who underwent the procedure[14].

Small-Molecule Therapies

In the past years, an accelerated development in psoriasis therapies has resulted in advanced targeted biological drugs. Methotrexate (MTX), cyclosporin A, and retinoids are traditional systemic treatment options for psoriasis. These all are oral drugs except for MTX, which is also available for subcutaneous administration. Dimethyl fumarate and apremilast, are newer drugs that have been approved for psoriasis. Table 1 presents different drugs which are currently used in clinics for the management of psoriasis in the range of the patients, their mechanism of action and route of administration.

Table 1: Different drugs in clinics for the psoriasis, mechanism and route of administration

Drug	Mechanism of action	Route of administration
Methotrexate	Dihydrofolate reductase inhibition blocks purine biosynthesis; induction of lymphocyte apoptosis	s.c./oral
Cyclosporin	Calcineurin inhibition leading to reduced IL-2	Oral
Acitretin	Normalization of keratinocyte proliferation/differentiation through retinoid receptor binding	Oral
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
Apremilast	PDE4 inhibitor increases in tracellularcAMP levels in immune and non-immune cell types modulating inflammation	Oral
Etanercept	Dimeric human fusion protein mimicking TNF-αR	s.c.
Infliximab	Chimeric IgG1κ monoclonal antibody that binds to soluble and transmembrane forms of TNF-α	i.v.
Adalimumab	Human monoclonal antibody against TNF-α	s.c.
Certolizumab	Fab portion of humanized monoclonal antibody against TNF-α conjugated to polyethylene glycol	s.c.
Ustekinumab	Human IgG1k monoclonal antibody that binds with specificity to the p40 protein subunit used by both the interleukin (IL)-12 and IL-23 cytokines IL-12/IL-23 p40	s.c.
Tildrakizumab	Humanized IgG1κ, which selectively blocks IL-23 by binding to its p19 subunit	s.c.
Guselkumab	Human immunoglobulin G1 lambda (IgG1λ) monoclonal antibody that selectively blocks IL-23 by binding to its p19 subunit	s.c.
Risankizumab	Humanized IgG1 monoclonal antibody that inhibits interleukin-23 by specifically targeting the p19 subunit	s.c.
Secukinumab	Human IgG1κ monoclonal antibody against IL-17A	s.c.
Ixekizumab	Humanized, immunoglobulin G4κ monoclonal antibody selectively binds and neutralizes IL-17A	s.c.
Brodalumab	Human monoclonal IgG2 antibody directed at the IL-17RA	s.c.

MTX is a folic acid analogue that inhibits DNA synthesis by blocking thymidine and purine biosynthesis. The initial recommended dose of 7.5–10 mg/weekly may be increased to a maximum of 25 mg/weekly depending on the efficacy and severity of the disease and patients responsiveness[15]. There is conflicting evidence regarding MTX effectiveness on psoriatic arthritis. Furthermore, HLA-Cw6 has been suggested as a potential marker for patients who may benefit from MTX treatment[16].The most common side effects include nausea, leucopenia, and liver transaminase elevation. Despite the potential side effects and its teratotoxicity, it remains a frequently used cost-effective first-line drug, and the close monitoring of liver function and full blood count make a long-term administration feasible.

Cyclosporine is a T cell-inhibiting immunosuppressant from the group of the calcineurin inhibitors. Cyclosporine is effective as a remission inducer in psoriasis and as maintenance therapy for up to two years[17].The dosage is 2.5 to 5.0 mg/kg of body weight for up to 10 to 16 weeks. Tapering of the drug is recommended to prevent relapse[17].Hypertension, renal toxicity, and non-melanoma skin cancer are significant potential side effects related to the duration of treatment and the dose. Cyclosporine is employed as an intermittent short-term therapy.

Retinoids are natural or synthetic vitamin A-related molecules. Acitretin is the retinoid used in the treatment of psoriasis. It affects transcriptional processes by acting through nuclear receptors and normalizes keratinocyte proliferation and differentiation [18].Acitretin is initially administered at 0.3–0.5 mg/kg of body weight per day. The maximum dosage is 1 mg/kg body weight/daily. Cheilitis is the most common side effect appearing dose dependently in all patients. Other adverse effects include conjunctivitis, effluvium, hepatitis, and teratogenicity.

Fumaric acid esters (FAEs) are small molecules with immunomodulatory and anti-inflammatory properties. It is thought to involve an interaction with glutathione, which among other mechanisms, inhibits the transcriptional activity of NF-κB[19]. DMF/MEF was approved in 1994 in Germany for the treatment of severe plaque psoriasis, and in 2008, the indication was expanded for moderate psoriasis[20].A marked improvement is also seen in patients with psoriatic arthritis and nail psoriasis. The most common side effects are gastrointestinal symptoms and flushing, which are generally mild in severity, resolve over time, and are dose related[21].In addition, FAEs may decrease lymphocyte and leukocyte counts. Therefore, it is recommended to perform a complete blood count before treatment initiation and monthly for DMF/MEF or every three months for DMF[21].

Apremilast,a phosphodiesterase-4 inhibitor, inhibits the hydrolyze-ation of the second messenger cAMP. This leads to the reduced expression of pro-inflammatory cytokines TNF-α, IFN0γ, and IL-12, and increased levels of IL-10. Apremilast was shown to have broad anti-inflammatory effects on keratinocytes, fibroblasts, and endothelial cells[22].No routine monitoring of hematologic parameters is required for apremilast, which is a major advantage compared to the other small molecule drugs. It is also effective for palmoplantar, scalp psoriasis, and nail psoriasis in addition to psoriatic arthritis[23].The most common adverse events affected the gastrointestinal tract (nausea and diarrhea) and the upper respiratory tract (infections and nasopharyngitis). These effects were mild in nature and self-resolving over time.

The traditional systemic drugs

These are mostly immunomodulators, which except for apremilast require close clinical monitoring due to the common side effects involving mainly the kidney and the liver. Methotrexate and cyclosporine are the only systemic therapies for psoriasis included in the World Health Organization (WHO) Model List of Essential Medicines, albeit for the indications of joint disease for the former and immunosuppression for the latter. The potential side effects of FAE and apremilast are usually not life-threatening, but might be sufficient to warrant discontinuation.

Biologics

In the context of psoriasis treatment, current use of the term biologics refers to complex engineered molecules including monoclonal antibodies and receptor fusion proteins. These biologics target specific inflammatory pathways and are administered subcutaneously(s.c.)(or intravenously i.e., infliximab) on different weekly schedules. This is main difference between biologics and small molecules. Biologics presently target two pathways crucial in the development and chronicity of the psoriatic plaque: the IL-23/Th17 axis and TNF-α-signaling (Table 1).

TNF-α inhibitors

TNF-αinhibitors have been available for over a decade and considered the first-generation biologics effective for plaque psoriasis and psoriatic arthritis. TNF-α inhibitors are still the standard used to evaluate drug efficacy in psoriasis clinical research[24]. There are currently four drugs in this category: etanercept, infliximab, adalimumab, and certolizumab.Etanercept is unique that it is not a monoclonal antibody, but rather a recombinant human fusion protein. The receptor portion for the TNF-α ligand is fused to the Fc portion of an IgG1 antibody. It was the first TNF-α inhibitor approved by the United States Food and Drug Administration (FDA) for psoriasis[25].

Infliximab is a chimeric monoclonal IgG1 antibody, and adalimumab is a fully human monoclonal IgG1 antibody. They neutralize TNF-α activity by binding to its soluble and membrane-bound form. These drugs are particularly employed to treat psoriatic arthritis, and show a similar efficacy. In the treatment of psoriasis, they show different PASI 75 response rates: 52% for etanercept, 59% for adalimumab, and 80% for infliximab. Infliximab shows superiority in terms of efficacy when compared to the other TNF-α inhibitors. The chimeric nature of infliximab might contribute to a higher immunogenic potential of the drug, which in turn might influence drug survival[25].

Certolizumabpegol is a pegylated Fab' fragment of a humanized monoclonal antibody against TNF-α. PEGylation is the covalent conjugation of proteins with polyethylene glycol (PEG), and is attributed a number of biopharmaceutical improvements, including increased half-life and reduced immunogenicity[26]. The initial indication for treating Crohn's disease was extended to psoriatic arthritis and recently to plaque psoriasis. Certolizumab has shown an 83% PASI 75 response. Since it does not actively transported across the placenta, certolizumabpegol is approved for use during pregnancy and breastfeeding psoriatic women.

***IL-23* targeted drugs**

Ustekinumabis the first biologic to be approved for psoriasis vulgaris after the TNF-α inhibitors in this category, which is a monoclonal antibody directed against the p40 subunit of IL-23. By targeting p40, ustekinumab blocks two different T-cell activating mechanisms, namely Th1 and Th17 selection. Ustekinumab is also effective for the treatment of PsA and Chron's disease. It is available in two dosages, 45 mg and 90 mg, depending on a threshold body weight of 100 kg. Ustekinumab has extensive safety data, few side effects, good clinical efficacy, and long treatment drug survival was reported. Studies using real-life data compared ustekinumab with the anti-TNF-α drugs, and ustekinumab was found to have a significant longer drug survival[27].Frequent adverse events include nasopharyngitis, upper respiratory tract infections, fatigue, and headache. Among the serious adverse events listed in the label of ustekinumab are infections. Tuberculosis (TB) has only been reported in two psoriasis patients receiving ustekinumab[28].The clinical efficacy of ustekinumab and the further clarification of its mechanism of action highlighted the crucial role of IL-23 in shaping the Th17 response.

Three fully human monoclonal antibodies with p19 specificity are available: guselkumab, tildrakizumab, and risankizumab. Guselkumab is licensed for psoriasis, and showed clinical superiority when compared to adalimumab[29]. IL-23 inhibition has the potential to modify the course of the disease after subsequent drug retrieval.

***IL-17* targeted drugs**

Three human monoclonal antibodies targeting IL-17 are available. Secukinumab and ixekizumab block IL-17A; whereas brodalumab is directed against the IL-17 receptor A. IL-17-targeted biologics are fast acting.

Secukinumab was the first IL-17A inhibitor approved for psoriasis in 2015. A year later, the approval extended to include PsA and ankylosing spondylitis. Secukinumab showed a rapid onset of action, reflecting a significant likelihood of achieving PASI 75 as early as the first week of treatment when compared to usteki-numab[30].

Ixekizumab also showed a significantly rapid onset of action in the first week when compared to placebo: a 50% PASI 75 response at week four, and 50% PASI 90 by week eight. At week 12, response rates were 89.1% for PASI 75 and 35.3% for PASI 100 [22]. Secukinumab and ixekizumab have proven effective for scalp and nail psoriasis, which are two clinical variants that are resistant to conventional topical therapies[31].

Brodalumab is a human monoclonal antibody that targets the IL-17 receptor type A, thus inhibiting the biological activity of IL-17A, IL-17F, interleukin-17A/F, and interleukin-17E (also called interleukin-25). Anti-IL-17 biologics should not be used in psoriasis patients also suffering from Chron's disease[32].

Drugs in the Research Pipeline

Tofacitinib is 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. Upadacitinib is another JAK inhibitor currently 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[33]. Two different biologics targeting IL-17 and one targeting IL-23 are being currently tested. In addition, there are currently 13 registered phase III clinical trials testing biosimilars for adalimumab (eight), infliximab (three), and etanercept (two).

Perspectives

Psoriasis is a complex multifactorial disease for which various novel therapies have arisen in the past years. In spite of the

refinement of the targeted therapies, psoriasis remains a treatable but so far not curable disease. An initial clinical response for many drugs is only short lived, requiring treatment with a different biologic. Clearly, more research is required to answer the question of why the drug survival of some biologics is limited. The therapeutic arsenal for psoriasis is likely to increase soon, with studies on orally applied new small molecules. Safety and efficacy of targeted therapies, dosage regimes, and adverse effect profiles, broader-acting drugs remain the mainstay of psoriasis systemic therapy in many clinical scenarios around the world. The role of genetics may play significant role in deciding on the selection of drugs based on cytokine signatures, and therapy response markers. After achieving excellent clinical responses for the majority of patients with available therapeutic approaches, the stratification of psoriasis patients to the optimal drug and ensuring the sustainability of our treatments are the major tasks to be resolved.

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