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Review

Emerging landscape in psoriasis management: From topical application to targeting biomolecules

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ABSTRACT

Psoriasis is a chronic autoimmune skin disorder affecting 2–3% of the world population. It has characteristic features such as increased keratinocyte proliferation and production of inflammatory mediators. The treatment involves various strategies including topical, systemic, phototherapy and biologics. Topical therapies are preferred for mild to moderate psoriasis conditions over the systemic therapies which are ideal in severe disease conditions. The systemic therapies include immunosuppressants, biological agents and recently approved phosphodiesterase-4 (PDE4) inhibitors. There are various limitations associated with the existing therapies where the new findings in the pathogenesis of psoriasis are paving a path for newer therapeutics to target at the molecular level. Various small molecules, PDE-4 inhibitors, biologics, and immunomodulator proved efficacious including the new molecules targeting Janus kinases (JAK) inhibitors that are under investigation. Furthermore, the role of genetic and miRNAs in psoriasis is still not completely explored and may further help in improving the treatment efficacy. This review provides an insight into various emerging therapies along with currently approved treatments for psoriasis.

1. Introduction

Psoriasis is a chronic autoimmune disorder associated with localized and generalized skin lesions and demarcated erythematous and silver scaly plaques. It is mainly characterized by impairment in keratinocytes proliferation and maturation, increased in dermal blood vessel formation and increase in inflammatory-mediated cytokines. Around the globe, 2–3% of the population is affected by psoriasis. According to the international review report, approximately 0.5–11.4% of adult and 0–1.4% of children population is suffering from psoriasis. Geographical conditions and genetic variation may impute differences in the pathogenesis of psoriasis. It was observed that populations located closer to the equator (Asian and African countries) being less affected by psoriasis compared with countries more distant from it (Europe and Australia) [1]. World health organization (WHO) 2016 report indicated that the population affected by psoriasis in China was 0.17% in 1984 whereas after 25 years it was found to be 0.59%. Similarly, in Spain it was 1.43% in 1984 and after 15 years it was reported as 2.31%. National health and nutrition exam survey report also indicated the increasing prevalence of the disease state as 1.62% to 3.10% from 2004 to 2010. In 2008, the estimated cost for psoriasis treatment was 11.5 million United States (US) dollars. Normally US patients spend an average of 2528 US dollars each year [2]. In a survey of national psoriasis foundation, a total population of 5600 patients, 28% given up with the provided treatment due to the factors such as high cost, discomfort and the inconvenience associated with the treatment [3,4]. This all indicated the severity of psoriasis and its impact on socio-economic aspects of the patients.

In psoriasis, the life cycle of skin is reduced to 1.5–3 days whereas normal skin it takes 30 days. Skin and nails are commonly affected by psoriasis conditions. It also includes various other comorbidities like psoriasis arthritis, diabetes, obesity, cardiovascular disorders, and metabolic syndrome [5]. It is found to be induced by T-cell mediated reaction and therefore also termed as T-cell mediated autoimmune disorder. In psoriasis, various inflammatory cytokines such as tumor necrosis factor (TNF-α), interferon-γ (IFN- γ) and interleukins (ILs) [IL-

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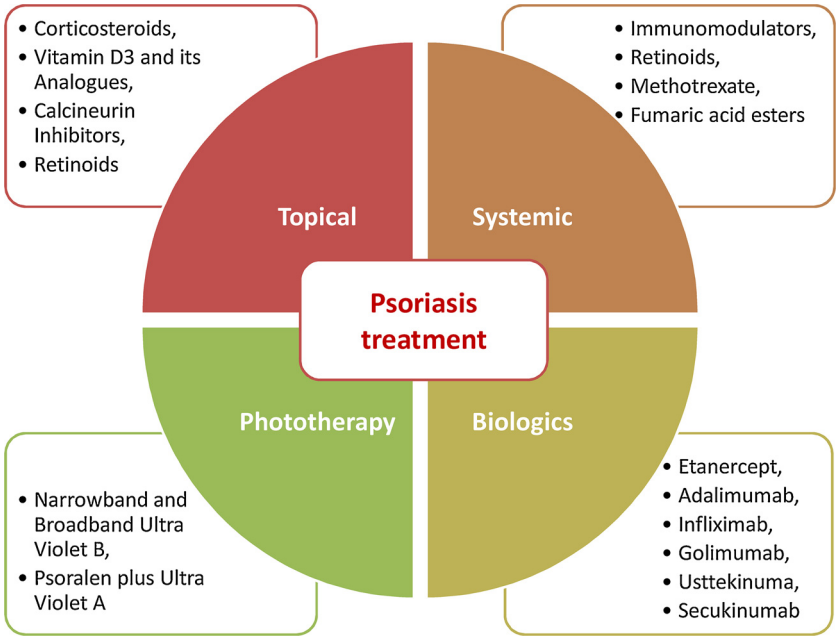

Fig. 1. Various treatment strategies for psoriasis.

1,2, 4, 6, 8, 12, 17, 18, 22 and 23] levels are predominantly increased in the dermis and a slight increase is observed in the systemic circulation [6,7]. Increase in cytokines level and other inflammatory mediators leads to the production of vascular endothelial growth factor (VEGF) by keratinocytes, mast cells, and macrophages which resulted in the formation of new blood vessels and increased blood flow [8]. Based on various recent investigations up to 25 genetic variants are responsible for psoriasis disorder [9]. Identification of the genes responsible for psoriasis may help in the cause of immune system activation. These findings may also help in the delivery of accurate and effective therapeutics for the treatment of psoriasis [10].

2. Treatment strategies for psoriasis

Psoriasis does not have a cure, but it is only been treated using various therapies to get relieved from the symptoms. Fig. 1 represents various treatment strategies include topical, systemic, phototherapy, and applications of biological agents. In mild to moderate psoriasis conditions (usually body surface affected by less than 10%), topical therapy is preferred as maintenance therapy. Whereas in severe disease conditions systemic therapy is preferred which includes immunosuppressants, biological agents and recently approved phosphodiesterase-4(PDE-4) inhibitors [11,12]. Traditional topical therapies include corticosteroids, vitamin D3 analogs, calcineurin inhibitors, retinoids, coal tar, dithranol, and emollients. In case of severe psoriasis condition, adjuvant phototherapy is combined with topical therapy i.e., narrow band ultraviolet B, broadband ultraviolet B, psoralen plus ultraviolet. Traditional systemic therapies include immunomodulators (cyclosporine), retinoids (acitretin) and miscellaneous agents like methotrexate, fumaric acid esters [13,14].

2.1. Topical therapy

Dry skin and irritation are common in psoriasis conditions. Moisturizers or emollients exhibit anti-inflammatory effects but they are not effective to the mark as monotherapy. Emollients act as an adjuvant to topical and systemic therapy. Topical therapy targets the keratinocytes proliferation, hyperkeratosis, immune cells and inflammation in the skin. Topical therapeutic agents for psoriasis and their mechanism are mentioned in Table 1. Long-term use of topical agents like corticosteroids leads to skin atrophy and adrenal axis suppression. Combination therapy is preferred when a single agent is not effective up to the mark. To overcome the adverse effects of monotherapy, a combination of two or more topical agents are indicated to improve the efficacy and reduce the side effects [15,16].

Dovobet®, a combination of calcipotriol and betamethasone exhibited improved efficacy with reduced skin irritation and faster onset of action with reduced dosage regimen (once in a day formulation) [17]. Some of the new chemical entities for topical therapy including icotinib hydrochloride cream (NCT03222622) for mild to moderate psoriasis is in phase II clinical trials [18], ARQ-151 cream 0.5%, and ARQ-151 cream 0.15% (NCT03392168) are also under phase I/II clinical studies [19]. A combination of halobetasol and tazarotene (IDP-118) lotion for plaque psoriasis (NCT02462122) is in phase III clinical trial [20]. Moreover, the combination of calcipotriol and niacinamide cream has completed phase II clinical trials [21]. All such clinical studies revealed the improved efficacy of combination therapy over conventional single drug therapy.

2.2. Nanocarriers in topical delivery of therapeutics

Conventional marketed topical formulations exhibit poor permeation through the skin in psoriasis leading to reduced efficacy, repeated application of the formulation and various side effects such as irritation. The concept of novel drug delivery systems such as nanoparticles for topical delivery in the treatment of psoriasis is under investigations and gaining massive attention [22–24]. Various nanocarrier based topical formulations are found to be more efficacious compared to conventional formulation due to increased permeation, controlled release, and protection from degradation in psoriasis conditions [24,25]. Nanocarriers are found to improve the efficacy of the topical therapeutics with reduced dosage regimen and dose of therapeutics. The *in-vivo* studies suggest nanocarriers as a preferred delivery system in case of psoriasis to improve permeation through the scaly skin [25,26].

Lapteva et al. investigated that *ex-vivo* permeation of tacrolimus loaded polymeric nanoformulation was found be significantly higher ($1.50 \pm 0.59\,\mu g/cm$) compared to conventional ointment ($0.47 \pm 0.20\,\mu g/cm$). The decrease of drug concentration in deeper skin layers indicated the delivery of tacrolimus to targeted superficial layers and reduced adverse effects with minimum systemic absorption