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## Potential Review for the Treatment of psoriasis

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### ABSTRACT:

Psoriasis is a common, chronic, relapsing, papulo-squamous dermatitis, with overlying silvery scales. Psoriasis is an autoimmune disease. Genetic and environmental factors play a important role in psoriasis. The most commonly affected sites are the scalp, elbows, knees, umbilicus, genitalia, sacrum and shins. Psoriasis affects 3% of the population of the world. First-line treatments are topical: emollients, dithranol, tar, deltanoids and corticosteroids. Second-line treatments have more side effects and include phototherapy and systemic drugs: methotrexate, cyclosporine, acitretin, hydroxycarbamide and fumarates. Biological therapies are costly and demonstrate immunosuppressant activity, and are currently reserved for patients unable to benefit from first-line and second-line modalities. We aim to briefly describe the biology of psoriasis, document the key features of treatments that are available or under development, and explain how these treatments can be used effectively to manage this chronic relapsing disease.

**KEY WORDS:** Psoriasis, Treatment, Autoimmune disease. Relapsing

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### INTRODUCTION:

#### EPIDEMIOLOGY

Although psoriasis occurs worldwide, its affects 3% of the world's population. 7.5 million American affected by psoriasis. The prevalence of psoriasis in adults ranged from 0.91 to 8.5 percent, and the prevalence of the disease in children ranged from 0 to 2.1 percent. There is no clear gender predilection for psoriasis. A retrospective study of a cohort of adults reported an increased incidence of psoriasis between the years 1970 to 1974 (50.8 cases per 100,000) and 1995 to 1999 (100.5 cases per 100,000). Another cohort study assessing the incidence of psoriasis in children also reported increasing incidence, from 29.6 cases per 100,000 to 62.7 cases per 100,000 during the same time periods. Although psoriasis can begin at any age, the disease is less common in children than adults. There seem to be two peaks for the age of onset: one between the ages of 30 and 39 years and another between the ages of 50 and 69 years.

#### HISTOPATHOLOGY

The characteristic histology of psoriasis is as follows. Hyperproliferation of keratinocytes gives rise to acanthosis thickening of the epidermis resulting from increased numbers of acanthocytes ('prickle cells'). This thickening occurs in ridges, with intervening areas of thinning occupied

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by elongated dermal papillae. Hyperproliferation is accompanied by incomplete differentiation and maturation, so that the cells are shed abnormally in large clumps.

Dilatation and elongation of capillaries occurs. These reach the top of the dermal papillae and almost penetrate to the surface of the skin.

Infiltration of the dermis and epidermis involves neutrophils, lymphocytes, macrophages and dendritic antigen-presenting cells. The neutrophils often form accumulations termed 'microabscesses of Munro' (in the stratum corneum) or 'micropustules of Kogoj' (in the upper epidermis).

**PATHOLOGY**

The pathogenesis of psoriasis is incompletely understood. The pathogenesis of psoriasis is difficult to elucidate. Psoriasis is a complex, multi-factorial disease that appears to be influenced by genetic and immune-mediated components. The theory is that it is an autoimmune disease in which epidermal and capillary proliferation result from release of cytokines by lymphocytes. The epidermis is infiltrated by a large number of activated T cells, which appear to be capable of inducing keratinocyte proliferation. This is supported by histological examination and immunohistochemical staining of psoriatic revealing large populations of T cells within the psoriasis lesions. One report calculated that a patient with 20% body surface area affected with psoriasis lesions has around 8 billion blood circulating T cells compared with approximately 20 billion T cells located in the dermis and epidermis of psoriasis.

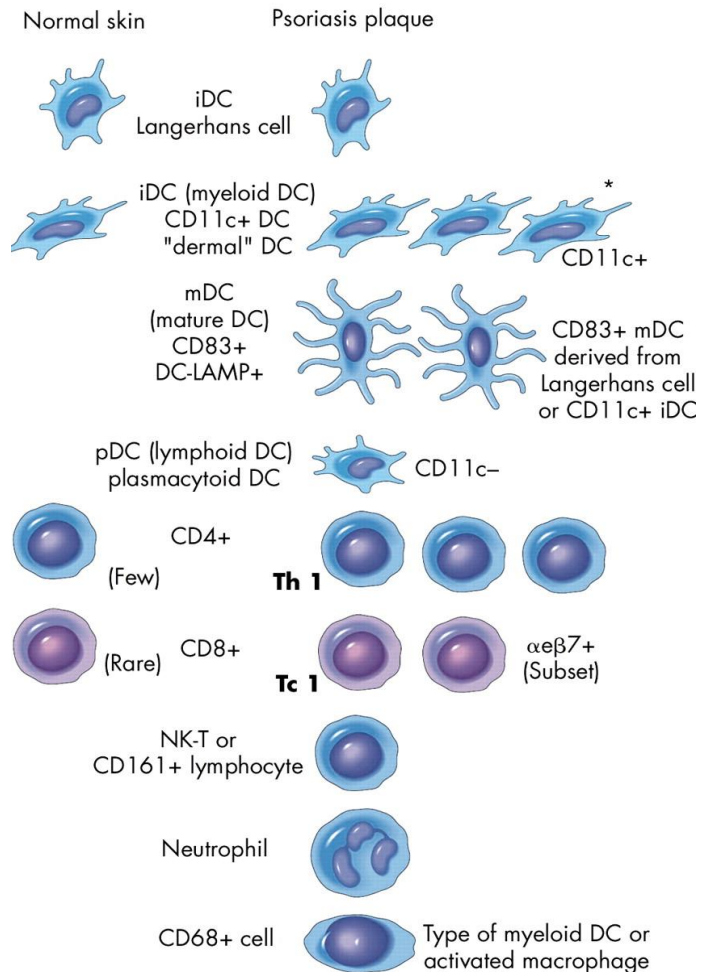
Deregulated inflammatory process ensues with a large production of various cytokines (e.g., tumor necrosis factor- $\alpha$  [TNF- $\alpha$ ], interferon-gamma, interleukin-12). Many of the clinical features of psoriasis are explained by the large production of such mediators. Interestingly, elevated levels of TNF- $\alpha$  specifically are found to correlate with flares of psoriasis.

**Etiology**

**Genetic factors**

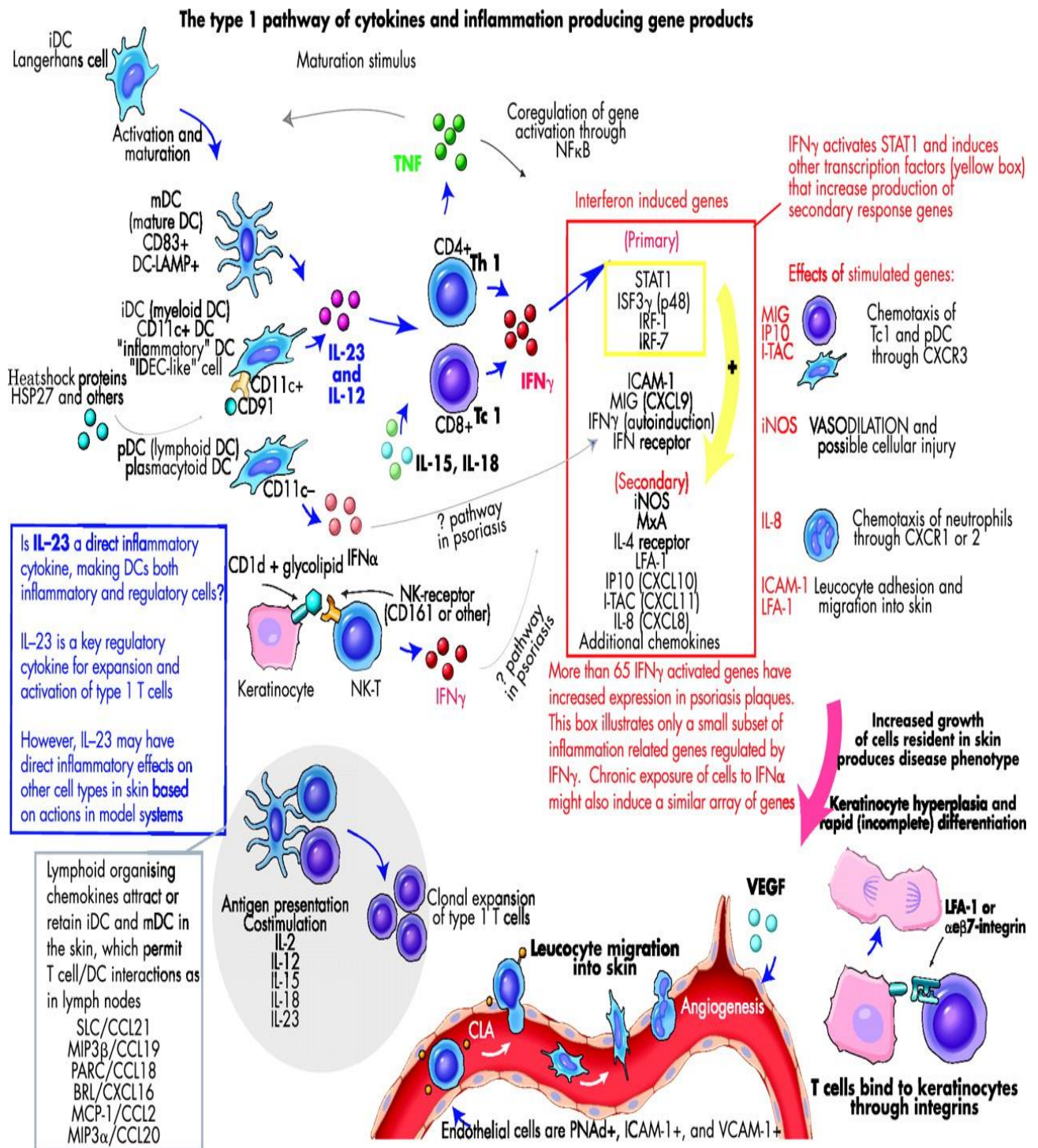
Patients with psoriasis often have affected relatives. Identical twins have a concordance rate of 56–70% in different studies, indicating that both genetic and environmental factors have a role. Further evidence for

an underlying genetic basis comes from the strong association of the disease with HLA-Cw6. There are weaker associations with human leukocyte antigen (HLA) B13, B17 and DR7. Both the HLA associations and a family history of psoriasis are more common in patients who develop the disease before the age of 40 years.



**Environmental factors**

Patients with psoriasis are more likely to smoke and have a higher alcohol intake than the general population. It remains controversial whether embarrassment engendered by psoriasis leads to these habits, or whether the smoking and alcohol may trigger or exacerbate the disease. Probably both are the case. Many patients state that stress induces flares in disease activity. Various drugs (notably lithium,  $\beta$ -blockers and antimalarial agents related to chloroquine) have been reported to induce exacerbations of psoriasis, but most patients can take these drugs without any effect on their disease. Withdrawal of systemic corticosteroids sometimes results in a flare of psoriasis. Oral contraceptives aggravate the disease in some patients



and improve it in others. Upper respiratory tract infections, particularly with streptococci, are associated with disease flares, particularly of the guttate type. HIV infection often aggravates psoriasis.

### Psoriasis in childhood

Children often have difficulty accepting that they have psoriasis. Moral support is required, and outpatient treatment in a dermatology department can be valuable

for this reason. In most children, psoriasis can be managed using topical treatment, though compliance is usually a problem. Use of topical corticosteroids should be avoided because this entails a lifetime of treatment, and excessive cumulative exposure results in cutaneous atrophy. Phototherapy is effective, but exposure to ultraviolet light is best minimized because excessive use can lead to subsequent cutaneous malignancies and photo-ageing. Retinoids or ciclosporin are probably the systemic agents of choice.

## Psoriasis and pregnancy

Psoriasis often improves during pregnancy. Less often, it flares dramatically, but then usually improves post-partum. Treatment is with topical modalities (except retinoid) or UVB when possible. Psoralen UVA is avoided because of concerns over teratogenicity. Most systemic treatments are potentially teratogenic, but ciclosporin is probably safe. Systemic retinoids are best avoided in female patients after puberty because of the risk of teratogenicity. Pregnancy should be avoided within 2 years of taking acitretin.

## Psoriasis in the elderly

Elderly patients usually need help when topical treatments are used. Phototherapy may be impractical for patients who are frail or cannot attend a clinic regularly. Methotrexate is often well tolerated, but smaller doses are required, partly because of renal impairment. Ciclosporin is usually not well tolerated because of limited renal reserve.

## TREATMENT OF PSORIASIS

### Topical treatment

#### 1. Tar

Crude coal tar is produced from the distillation of coal at temperatures between 900°C and 1200°C. A thick, black by-product of the manufacturing of petroleum products. Coal tar is probably the oldest product treatment for psoriasis. It reduces scaling, itching, and inflammation. Tar appears to exert its actions through suppression of DNA synthesis and subsequent reduction of mitotic activity in the basal layer of the epidermis. Tar can help slow the rapid growth of skin cells and restore the skin's appearance. It acts as a keratolytic, which works to break down a protein which forms part of the skin structure called keratin. Skin thickening occurs due to the deposition of keratin. Coal tar helps to reduce the excessive, hardening, thickening, scaling of skin.

#### 2. Retinoid

Topical retinoid analogues help normalize hyperkeratinization and have demonstrated anti-inflammatory effects. Retinoids are potent agents that can normalize abnormal growth and differentiation in keratinocytes. Topical retinoids also demonstrate inhibition of various immune factors, inducing the activity

of leukocytes, the release of pro-inflammatory cytokines. Tazarotene gel is a third-generation acetylenic retinoid and has been licensed for use in psoriasis. A large study of 324 patients treated with tazarotene (0.05%, 0.1%, and placebo) demonstrated a decrease in psoriasis.

#### 3. Corticosteroids

Corticosteroids have played a prominent role in the treatment of psoriasis for the past 50 years. Mild to moderate potency corticosteroids remain first-line treatment for involvement of the face, flexures, and genitals. Topical corticosteroids are now frequently used in combination with other forms of topical treatment such as vitamin D analogues. Potent corticosteroids have been shown to be as effective as calcipotriol, but calcipotriol was less effective than superpotent corticosteroids. In a 2-week trial, combination of calcipotriol and a superpotent corticosteroid achieved clearance more frequently than either treatment alone. When topical corticosteroids are used in combination with PUVA, they achieved more rapid rates of clearance than PUVA alone, but in combination with crude coal tar and UVB, they were associated with an earlier relapse. Compared with dithranol therapy alone and in combination of betamethasone valerate and showed that the rate of relapse was significantly shorter with the combination therapy. A particular problem with corticosteroids in treating psoriasis is tachyphylaxis with repeated use.

#### 4. Dithranol

Dithranol remains one of the oldest treatments used for psoriasis. Dithranol up-regulates interleukin-10 receptor expression on keratinocytes, which may be one of the mechanisms by which dithranol produces its therapeutic action. Dithranol is most suited to large stable chronic plaque disease and is particularly effective in an inpatient setting often combined with UVB (Ingram regimen). For outpatient use, many patients prefer the short-contact dithranol regime, which has been developed based on the finding that dithranol is absorbed into psoriatic plaques more quickly than the surrounding skin. If dithranol is removed after 30–60 min, less perilesional irritation is produced without reducing efficacy. Its drawbacks include irritation of perilesional skin and staining of skin and household items. In an open comparative study of 478 patients, short-contact dithranol at the highest strength tolerated was compared against calcipotriol ointment. The mean psoriasis area



and severity index (PASI) fell from 9.1 to 4.7 after 8 weeks of treatment on dithranol and from 9.4 to 3.4 on calcipotriol.

5. Vitamin D analogues

Vitamin D is important in cellular and systemic Ca<sup>2+</sup> metabolism, but it also inhibits keratinocyte differentiation and proliferation, suggesting a role in the treatment of hyperkeratotic skin disease. Furthermore, it produces a shift towards Th2 cytokine expression, with an increase in IL-10 and a decrease in IL-8, which may mediate part of the improvement in psoriasis. The clinical use of vitamin D has been limited by hypercalcaemia and has driven the development of analogues of vitamin D with less effect on Ca<sup>2+</sup> + homeostasis. Calcipotriol binds with the same affinity to vitamin D receptors as vitamin D but is 100 times less active on systemic Ca<sup>2+</sup> + metabolism due to its rapid local metabolism. In a recent randomised, double-blind, controlled trial, once-daily calcipotriol (50 mg/g) was compared against a twice-daily regimen and calcipotriol alternating with clobetasone 17-butyrate and calcipotriol with betamethasone-17 valerate. According to the investigators' overall assessment, 28% achieved clearance in the calcipotriol/vehicle group, 40% in the calcipotriol/ calcipotriol group, 42% in the calcipotriol/clobetasone group, and 54% in the calcipotriol/betamethasone group. Early studies of topical calcitriol at concentrations of up to 15 mg/g demonstrated asymptomatic hypercalcaemia. More recent experience with 3 mg/g formulation showed clearance in 48% of the patients treated with calcitriol in comparison with 7% of placebo, and a further 41% had a considerable improvement Tacalcitol (1 $\alpha$ ,24-dihydroxyvitamin D3) is also available in the United Kingdom.

6. Phototherapy

Ultraviolet light is a highly effective treatment, but is carcinogenic (causing mainly squamous cell carcinoma). Accurate monitoring and recording of doses combined with precise calibration of equipment is essential to minimize this risk and maximize efficacy. UVB comprises light of wavelength 290–320 nm. Traditionally, fluorescent tubes emitting a broad band of wavelengths have been used, but there is a current trend towards use of narrow-band UVB with fluorescent tubes emitting wavelengths of mainly about 311 nm. Eliminating shorter wavelength UVB increases efficacy and reduces the risk of burning. It is not yet clear whether carcinogenesis is reduced compared to treatment with broadband UVB. UVA (320–400 nm) is minimally effective in the treatment of psoriasis when used alone, but becomes highly effective when combined with photosensitizing psoralen. Psoralen is most often administered orally, but can also be applied topically a useful approach when limited areas such as palms and soles are treated. Bath PUVA involves a 20-minute soak in a bath of psoralen solution before UVA exposure. This avoids systemic exposure to psoralen and the nausea that some patients experience after oral therapy.

7. Emollient

Emollients provide a safe and useful adjunct in the treatment of psoriasis. Optimizing skin hydration is universally recognized to improve signs and symptoms of psoriasis. Clinical trials involving topical corticosteroids demonstrated a placebo response of 15-47%, indicating that the emollient effect of the vehicle provides a significant therapeutic benefit. The choice of emollient will be guided by the severity of xerosis and the preferences of both the clinician and patient. The emollient is generally applied 1-3 times a day. There are no known contraindications to emollient therapy, and emollients are regarded as safe in children, pregnancy and breast-feeding.

**Differential diagnosis and management of variants of psoriasis**

Variant	Differential diagnosis	Management
Guttate psoriasis	Pityriasis versicolor, pityriasis rosea	Topical treatments, UVB; when associated with recurrent tonsillitis, tonsillectomy may be helpful

Hand and Feet	Endogenous hand eczema, contact dermatitis, dermatophytosis	Avoid exposure to irritants (soap and detergents); emollients;  topical corticosteroids (potent or very potent) occlusion can be  used to increase the effect if necessary, but increases side-effects; calcipotriol, psoralen UVA, systemic agents
Palmoplantarpustular psoriasis	Pompholyx, dermatophyte infection	Topical antipsoriatic agents, low-dose ciclosporin, acitretin
Generalized pustular psoriasis	Acute exanthematous toxic pustuloderma	Urgent admission to hospital, bed rest, supportive care, emollients, topical corticosteroids, vitamin D analogues, systemic therapy
Erythrodermic psoriasis	Drug eruptions, various types of eczema, cutaneous T cell lymphoma, pityriasis rubra pilaris, ichthyoses	Bed rest in hospital, attention to hydration and body temperature, emollients, topical corticosteroids, systemic treatment
Nail involment	Pitting – dermatitis, alopecia areata Onycholysis – drug reaction, phototoxic reaction during psoralen UVA therapy Subungual hyperkeratosis – dermatophyte infection (may coexist with psoriatic nail dystrophy)	Topical corticosteroid lotion, intralesional corticosteroid injection, calcipotriol lotion, psoralen UVA
Flexural and genital psoriasis	<i>Candida</i> infection, erythrasma, seborrhoeic dermatitis, contact allergic dermatitis, benign familial pemphigus (Hailey–Hailey disease)	Tar extracts, calcitriol, tacalcitol, corticosteroids (moderately potent), antifungal/corticosteroid combinations (e.g. <i>Daktacort</i> cream)
Scalp psoriasis	Seborrhoeic dermatitis, ringworm, contact allergy	Tar shampoos (leave in contact for at least 15 minutes), corticosteroid lotions, emollients (e.g. coconut oil used overnight scale can then be combed out in the morning), tar, dithranol,  <i>Cocoi</i> sointment (12% tar with sulphur and salicylic acid, applied overnight under occlusion with a shower cap)
Facial psoriasis	Seborrhoeic dermatitis, contact dermatitis, atopic dermatitis	Mild/moderate topical corticosteroids, tar extracts, emollients, calcitriol, tacalcitol, tacrolimus (topical)

**Systemic treatments in psoriasis**

Drug	Advantages	Disadvantages
<b>Acitretin</b>	Relatively safe, except in fertile women	Teratogenicity, slow onset of action, cracked lips, hair thinning (reversible), raised plasma lipids
<b>Calcisporin</b>	Rapid action (improvement seen within 2 weeks), highly effective	Nephrotoxicity, hypertension, immunosuppression, relatively high cost
<b>Hydroxycarbamide(hydroxyurea)</b>	Can be used in patients with mild renal or hepatic impairment	Marrow suppression
<b>Methotrexate</b>	Highly effective, very low cost	Nausea, marrow suppression, hepatic fibrosis; hazardous in patients with renal or hepatic impairment
<b>Fumaric acid esters</b>	Relatively safe	Slow onset of action; flushing, diarrhoea and lymphopenia

**Biological agent for psoriasis**

Drug	Advantages	Disadvantages
<b>Adalimumab</b>	No organ-specific toxicity	Immunosuppression Need for subcutaneous

	Effective in treating psoriatic arthropathy	injection High cost
<b>Etanercept</b>	No organ-specific toxicity Effective in treating psoriatic arthropathy	Immunosuppression Need for subcutaneous injection High cost
<b>Infliximab</b>	Few side effect rapid action Effective in treating psoriatic arthropathy	Immunosuppression Need for intravenous infusion High cost
<b>Ustekinumab</b>	Low toxicity	High cost Immunosuppression subcutaneous injection

**CONCLUSION**

Psoriasis is a common, chronic inflammatory disease of the skin characterized by keratinocyte hyperproliferation and disordered differentiation with epidermal thickening and scaling. Paracrine and possibly direct interactions among keratinocytes and immune cells are central to psoriasis pathogenesis. Recent advances in immunology and genomics have revealed important roles for the innate immune system and the IL-23/Th17 axis in psoriasis and other immune-mediated disorders. Immune cells that play important roles in psoriasis include T cells, dendritic cells, macrophages, neutrophils, NK cells and mast cells. Over the past 20 years, our understanding of the disease mechanisms underlying psoriasis has advanced greatly, but many of the clinical phenomena observed in psoriasis remain enigmatic. Over the same time period, several effective treatments have been developed, but treatment is often hindered by inconvenience to the patient or toxicity.

The prospect of inducing remission with agents that specifically deplete pathogenic T-cells and maintaining that remission, perhaps with costimulation inhibitors, offers great hope for the future. It is anticipated that as

we develop a better understanding of the nature of genetic heterogeneity in psoriasis, we may be able to predict the response of a particular individual to a variety of treatments and to design more rational therapeutic strategies.

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