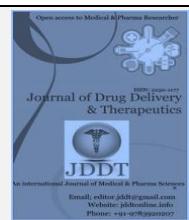


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Review Article

Immunomodulators in the Treatment of Psoriasis

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ABSTRACT

Psoriasis is a chronic T lymphocyte mediated systemic inflammatory disease characterised by recurrent exacerbations and remission of thickened, erythematous and scaling plaque and multiple comorbidities. Based on morphology and extend of involvement dermatosis may range from innocuous lesion to wide spread life threatening pustular and erythrodermic forms. Psoriasis is a multifactorial skin disease and it involves a complex pathogenesis. It can be explained by a immunological disregulation of cell function along with differentiation or proliferation of keratinocyte. Psoriasis treatment aims to reduce skin inflammation and to clear skin. Conventional therapy usually includes topical, light and systemic medications. All the three therapies are found to be good for the treatment but are associated with a number of side effects like increased skin sensitivity, burning, skin staining, xerosis and alopecia etc. Nowadays various recent therapeutic advances are attempting to control the T cell expression by the suppression of same and are correlates with the clinical remission. Immunomodulators and biological therapy contribute a new way for psoriasis therapy. These drugs are more safer, effective and selective immunosuppressive agents as compared to conventional agents. This review summarises the various immunomodulators used in the treatment of psoriasis

Keywords: Psoriasis, conventional therapy, immunomodulators

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INTRODUCTION

Psoriasis is a chronic T lymphocyte mediated systemic inflammatory disease characterised by recurrent exacerbations and remission of thickened, erythematous and scaling plaque and multiple comorbidities.¹

It affects usually 0.5-1.5% individual worldwide and are characterised by erythematous scaly plaque involving the scalp and extensors of limb. The affected individual may suffer from physical psychological and social morbidity. Based on morphology and extend of involvement dermatosis may range from innocuous lesion to wide spread life threatening pustular and erythrodermic forms. Palms, soles and genitalia are the common affected sites.²

PATHOGENESIS

Psoriasis is a multifactorial skin disease and it involve a complex pathogenesis.³ It can be explained by a immunological disregulation of cell function along with differentiation or proliferation of keratinocyte.⁴

An array of factors which are known to be involved in the disease pathogenesis are antigen presenting cell(APC), T cells, keratocytes, langerhans cells, macrophages, natural killer cells, Th1 type cytokines, growth factors like vascular endothelial growth factors, keratocyte growth factors.³ Th1 and Th17 plays a key role in disease pathogenesis.⁴

Any unknown antigen causes T cell activation which leads to the secretion of cytokines. Keratocyte proliferation is responsible for the characteristics psoriatic lesion.³ The naive cell get presented with antigen by activated langerhans cell. Recently developed animal models and studies provided new evidence for role of pathogenic lymphocyte in the initiation of disease.⁵

A recently discovered class of posttranscriptional regulators of gene expression called microRNA have critical function in health and disease.⁶

CONVENTIONAL THERAPY

Psoriasis treatment aims to reduce skin inflammation and to clear skin. Conventional therapy usually includes topical, light and systemic medications.

Topical treatment: Mild to moderate psoriasis can be effectively treated using creams and ointments. Topical medications can be combined with oral or light therapy if the disease is more severe in nature. Topical treatment includes use of topical corticosteroids, vitamin D analogue, anthralin, topical retinoid, salicylic acid, coal tar and other moisturizers. Even though these agents are used, are associated with adverse effects like increased sensitivity towards sunlight, skin irritation, and itching or stains skin.^{7,8}

Light therapy (Phototherapy): Use either natural or artificial ultraviolet light. It involves exposure of skin to controlled amount of light. Most common type of light therapy includes ultraviolet A (UVA) and ultraviolet B (UVB), either alone or in combination with medication. Along with this Goerckerman therapy (combination of UVB with coal tar), PUVA therapy are also used. This kind of light therapy are associated with both short term and long term side effects including nausea, headache, burning, itching, dry and wrinkled skin, freckles, increased sun sensitivity and increased risk of skin cancer including melanoma.⁹

Systemic therapy: If a patient suffering from severe psoriasis or he is resistant to any other therapy, systemic therapy is the drug of choice. Systemic therapy critically involves use of injections and oral medication, and it includes retinoids, methotrexate, acitretin and so on. They are teratogenic and should be avoided in pregnancy and other adverse effects include elevated serum lipid, gereralisedxerosis and alopecia.¹⁰

IMMUNOMODULATORS

Various recent therapeutic advances are attempting to control the T cell expression by the suppression of same.¹¹

TNF α inhibitors: it includes etanercept, infliximab and adalimumab.

1. **Etanercept:** it is an USFDA approved TNF α inhibitor .it is a recombinant DNA made fusion protein. It fuses to the IgG1 antibody. Both macrophages and lymphocyte produces this cytokine called TNF α . Which in turn mediate immune mechanism by attracting WBCs to the site of inflammation that intiate and amplify inflammation.^{12,13}
2. **Infliximab:** A chimeric monoclonal antibody, given as aslow injection to vein in an interval of 6-8 days. Infliximab have high affinity towards TNF α ,there by neutralizes the activity by binding to it and to other transmembrane forms. It also have the capacity of lysing cells involved in the inflammatory process.^{14,15}
3. **Adalimumab:** It is a subcutaneous injection generally recommended to non responders. Adalimumab binds to TNF α and inhibit it interaction with p55 and p75 and also lyses the cell which express surface tumor necrosis factor in the presence of a compliment. The benefit of using adalimumab in psoriasis is that it decreases inflammatory skin infiltration and epidermal thickness. In addition it alters the biological responses regulated by TNF.¹⁶

Efalizumab

A recombinant humanised monoclonal antibody, once in a week dose and given subcutaneously.¹⁷ Target for

efalizumab is CD11a; a lymphocyte function associated antigen 1 and it is an immunosuppressant. It acts by inhibiting activated lymphocyte and the cell migration to the tissue from blood vessels.¹⁸

It may associated with bacterial sepsis, viral meningitis, invasive fungal infections and progressive multifactorial leukoencephalopathy (PML) caused by JC virus infection.^{19,20} In a group of 500 patients treated with efalizumab, four reported to have PML.¹⁸

Alefacept

A genetic engineered immunosuppressive drug. It interferes with lymphocyte activation and thud used to control inflammation with plaque formation. Being a fusion protein it combines with a protein of antibody which in turn blocks the T cell growth and activation.

It act by dual mechanism- one is to inactivate CD4+ and CD8+ T cell by interfering CD2 on T cell membrane thus block co stimulatory molecule LFA-3/CD2 interaction. Another is to induce apoptosis of memory effectors T lymphocyte. 7.5 mg iv or 15 mg iv for 12 week is the usual dose of alefacept.²¹

Interleukin

They are the group of cytokine that are first expressed in WBC. Human genome encodes more than 50 IL and related protein.²² In the pathogenesis of psoriasis, aberrant type 1 immune response has been linked like IL-12 and IL-23, so they represent appropriate therapeutic targets.²³

IL-12 p40 is over expressed in psoriatic plaque. So in order to block IL-12 and IL-23 a fully human IL-12/13 monoclonal antibody (CANTO12/3) was developed. It is having high affinity towards P40 subunit of IL-12 neutralizing the bioactivity.²⁴

Denileukin

Denileukin Diftitox, fusion protein which target both normal activated and malignant T cell thus showing antipsoriatic activity. It is an engineered protein combination of IL-2 and diphtheria toxin. It involves killing of cell by introducing the diphtheria toxin into IL binding

ABX-IL-8

Fully human monoclonal antibody that target IL-8. It is widely approved in China

ABX-IL-8 bind to human IL8 with high affinity which make it unable to cross-react to chemokines. It also blocks binding of IL8 to IL8 receptor and inhibit IL8 dependent neutrophil activation migration and degranulation.²⁵

Apremilast

It is a phosphodiesterase 4 inhibitor (PDE4); orally administered drug that used in management of both plaque psoriasis and psoriatic arthritis.²⁶ PDE4 has role in immune regulation by cAMP degradation. It cause cAMP accumulation that in turn modifies the downstream signalling of pathways of both innate and adaptive immune system.²⁷

As a result the TNF α and IL-23 decreases and increase in anti-inflammatory mediators like IL-10 occurs. Daily recommended dose is 30 mg BD, 10 mg morning dose with daily increment of 10mg until 6th day then same dose thereafter.²⁸

CONCLUSION

Psoriatic patient suffer from physical, social and psychological co-morbidities; and they tend to get abscond from their social activities due to depression and stress. Although there are many different treatment options, they often have major side effects. Immunomodulators and biological therapy contribute a new way for psoriasis therapy. As clinicians and researchers build upon this knowledge in the years to come, we can offer psoriasis patients an increasingly diverse and powerful therapeutic armamentarium.

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