Treatment of Psoriasis - the promise of new 'biologicals'

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Abstract: **Psoriasis is a chronic, recurrent immune-mediated inflammatory dermatosis. Epidermal hyperplasia and infiltration of inflammatory cells into the dermis and neovascularization characterize this disease. The global prevalence rate is about 2-3%. It impairs the quality of life negatively, due to chronic complications and comorbidities like arthritis, cardiovascular issues, depression and metabolic disorders. The molecular mechanisms involved in psoriasis are complex, and deregulation of T-helper cells Th-1/Th-2/Th-17/Th-23 axis is implicated in the pathogenesis of the disease. Current treatment protocols for this disease have not been satisfactory. Biotechnological innovations have made possible the development of several new systemic therapies for psoriasis. 'Biologicals' are a new group of compounds including monoclonal antibodies, fusion proteins and recombinant proteins. Targets for the therapeutic strategies adopting the new 'biologicals' include inactivation of soluble mediators like tumor necrosis factor alpha, blockade of receptors for cytokines, adhesion molecules and interference with T-cell activation by antigen-presenting cells. About forty 'biologicals' are under examination for the management of psoriasis. Recombinant cytokines are in use to modulate immunological balance, as a therapy for psoriasis. This work reviews the recent developments in the treatment of psoriasis with new 'biologicals'.**

INTRODUCTION

Psoriasis is an inflammatory disease. It is chronic, recurrent and immune-mediated. It affects about 2-3% of world population (Dogra and Mahajan 2016). The prevalence rate of Psoriasis is estimated to be varying between 0.44% and 2.8% in our country. Psoriasis affects the male population more than the female population (Dogra and Yadav 2010).

It is characterized by chronic inflammatory skin lesions of five types predominantly – plaque, guttate, inverse, pustular and erythrodermic. The most common form is plaque. Psoriatic plaques appear as raised and red patches covered with dead cells (Devrimci-Ozguven et. Al., 2000). Often itchy and painful, there is risk of cracks and bleeding affecting the quality of life. Patients suffering from this disease are often subjected to social stigma and humiliation, leading to anxiety and depression. It has a high impact on the motional and psychological aspects of the patients (Kim et.al., 2017), making it compulsory to adopt suitable management protocols (Dauden et.al., 2016).

The aetiology of this disease is unclear. At present, consensus about the manifestation is that it is T-Cell mediated and influenced largely by genetic and environmental factors (Kanwar et.al.,2010). Since therapeutic choice for this multifactorial disease is not easy, marketed formulations that encompass all the needs of a psoriasis patient are currently unavailable. The most common approach for clinical management of Psoriasis is use of a combination of topical and oral formulations, all of which aim at reducing plaque formation. Corticosteroids, keratolytics, tazarotene, anthralin and calcipotriol are widely being used in the currently available therapies (Menter et.al., 2008). But, many side effects have been observed, resulting in therapeutic dropouts (Korman et.al., 2015; Sarma 2017). In addition, higher treatment cost is of concern amounting to 10 billion euros per annum and 40% work loss (Melnikova 2011). At present, routine clinical pracrice includes use of methotrexate (MTX), cyclosporine, acitretin, and small molecules, like apremilast (Armstrong et.al., 2013; Afra et.al., 2019), but many adverse effects have been reported from time to time (Fieldman et.al., 2016)

In this context, there arises an urgent need for development of new therapies for effective treatment regimes.

Biotechnological interventions

Biotechnological innovations made the development of new systemic therapies for Psoriasis. A new group of chemicals called biologicals seem to be promising. These include monoclonal antibodies, fusion proteins and recombinant proteins. These offer designer drugs to interact with specific targets and thus are safer (Graciliana Lopes et.al., 2020). Targets for these biologicals include blockade of cytokine receptors, inactivation of soluble mediators of the immune system, interference with T-cell activation etc. Currently, up to forty agents are under investigation for the treatment of psoriasis. Four of these agents, alefacept, efalizumab, etanercept and infliximab have already impacted on routine clinical practice. These 'biologicals' appear to be promising in combating Psoriasis. Current developments in the treatment of psoriasis with biologicals are briefly reviewed.

Table 1 – List of some of the biologicals currently used in clinical practice for treatment of Psoriasis

Sl.No	Name of the 'biological'	Target/mechanism of action
1	Adalimumab (Humira)	TNF-alpha-blocking antibody
2	Adalimumab-adbm(Cyltezo)	biosimilar to Humira
3	Brodalumab (Siliq)	human antibody against interleukins
4	Certolizumab pegol (Cimzia)	TNF-alpha blocker
5	Etanercept (Enbrel)	TNF-alpha blocker
6	Etanercept-szzs (Erelzi)	A biosimilar like Enbrel
7	Guselkumab (Tremfya)	an antibody against interleukins
8	Infliximab (Remicade)	TNF-alpha blocker
9	Ixekizumab (Taltz)	An antibody that binds to inflammation-causing proteins/interleukins
10	Risankizumab-rzaa (SKYRIZI)	an antibody against interleukins
11	Secukinumab (Cosentyx)	A human antibody against interleukins
12	Ustekinumab (Stelara)	A human antibody against interleukins

These biologicals are used according to the international guideline recommendations and literature evidence (AAD 2008, AAD 2019, BAD 2017, European S3,) and protocol (Rajagopalan and Mital 2016).

Therapeutic approaches and challenges with biologicals

In the recent past, new biological therapies with are developed. Their mechanism of action involves more precise targets (porter et.al., 2017). First generation biologicals are developed targeting tumour necrosis factor (TNF-α). These include etanercept, infliximab, and adalimumab. These are used for patients who suffer from chronic moderate-to-severe psoriasis. From 2009 onwards, Second-generation biologics emerged. Their mechanism of action involves antibody targeting the IL-23/Th17-pathway. Examples include ustekinumab, secukinumab, ixekizumab, brodalumab, guselkumab, risankizumab, and tildrakizumab.

Secukinumab is the only second-generation biologic available in India at present. It is It is indicated as the first-line systemic in moderate-to-severe plaque psoriasis in adult patients (Rajagopalan et.al., 2021).

Clinical challenges in using biologicals

At present, only a limited evidence available is available about the practical issues faced with biologicals usage. Data available so far is inconsistent to arrive at a conclusion for primary failure or secondary failure and the management in such cases. Expert consensus are available for different countries, which can be used as a guide for clinicians.

CONCLUSION

New biologicals are emerging as a hope for patients suffering from psoriasis. But, there is need to evolve country-specific recommendations.

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