Psoriasis is a chronic inflammatory and multifactorial systemic disorder with predominant manifestation over the skin and/or joints resulting from interactions between genetic pre-disposition and triggering environmental factors. Due to its systemic nature, patients exhibit a broad spectrum of symptoms that vary in severity. Although many patients, particularly those with the limited form of the disease, may be treated with topical therapy, those with extensive (moderate to severe) psoriasis eventually require phototherapy, systemic, or biologic therapy to adequately suppress the systemic, immunopathogenic process. Biological agents (biologics or biologicals) are a set of different engineered proteins. These are immunosuppressive agents, designed to selectively interfere with the immune mechanisms that induce psoriasis. Their use is restricted to the treatment of moderate to severe psoriasis, which has failed to respond to systemic therapies (and/or phototherapy) or where such treatments are contra-indicated or not tolerated. Biologics are becoming increasingly useful for the treatment of many skin diseases including psoriasis, particularly as alternatives for patients who have failed to tolerate or respond to conventional systemic therapies or where non-biologic systemic agents are unsuitable due to the presence of comorbidities. Biological therapies provide a targeted approach to treatment through interaction with specific components of the underlying immune and inflammatory disease processes.

Keywords: Immunopathogenesis, Biologicals, Psoriasis, Quality of life, Psoriasis area and severity index, Dermatology life quality index.

INTRODUCTION

Psoriasis is a disorder with multiple different phenotypical variations and degrees of severity. Approximately 80% of patients with psoriasis have milder to moderate disease, whereas 20% have severe disease. The severity of psoriasis is defined not only by extent of body surface area involved but also by the involvement of particular site such as hands, feet, face, or genital regions, because despite the involvement of a smaller body surface area, the disease may interfere significantly with activities of daily life or quality of life [1].

The onset of psoriasis predominantly occurs early in adulthood (between the ages of 15 and 25 years) but may affect individuals at any age [2]. The course of psoriasis is marked by chronic and acute phases with a wide variety in relapse and clearance rates [3].

Both genetic and environmental factors contribute to the development of psoriasis. Its pathogenesis is a complex interplay between environmental factors and genetic predisposition. Hyperproliferation of epidermal keratinocytes, the dysregulated interplay between epidermis and dermis, cutaneous microvasculature, and immune system results into scaling, thickened plaques, and erythema of the skin [4]. Several studies have demonstrated the presence of discrete populations of Th1 and Th17 cells in psoriatic skin lesions, confirming the significance of T-cell mediated immune responses in the disease process. Many of the genes identified as conferring susceptibility to psoriasis belong to the interleukin-23 (IL-23)-Th17 axis, the NF-κB pathway, and the epidermal differentiation complex [5].

Topical therapies, such as topical corticosteroids, vitamin D analogs, dithranol, and tar preparations, are used as first line treatment and can be prescribed in primary care. Second line therapy includes phototherapies, i.e., broad or narrow-band ultraviolet B-light and psoralen plus ultraviolet A (UVA) therapy (psoralen plus UVA light) and systemic non-biological agents such as methotrexate and usually should be prescribed by a specialist dermatologist. Biological agents such as adalimumab, etanercept, and infliximab are usually prescribed by a specialist dermatologist in secondary or tertiary care settings.

The biologics can be used in combination with non-biologics and or phototherapy as per need. The treatments recommended by specialists may change based on the progress of the symptoms due to the lapsing and remitting nature of psoriasis [6].

Nomenclature of biologicals

Biologics can be divided into three main groups, which are monoclonal antibodies, fusion proteins, and cytokines. Generic names of chimeric monoclonal antibody end with - Ximab. These are derived from variable region of donor mouse mAb grafted onto acceptor human antibody. Humanized monoclonal antibody end with - Zumab. These are complementarily determining region segments from the variable region of donor mouse mAb grafted onto acceptor human variable region. Human monoclonal antibodies end with - Umab. These are Human monoclonal antibody from fully human mAb, no mouse components. Receptor antibody fusion proteins end with - Cept. These molecules react mainly with cell surface molecules expressed selectively on leukocytes or with molecules secreted by inflammatory cells [7,8].

Biologics directed at selected targets integral to the pathogenesis of psoriasis are the logical progression of the biotechnological revolution as applied to a more detailed knowledge of the roles of T-cells, their differentiation pathways and pro-inflammatory cytokines in psoriasis. Several of these therapies are now in widespread clinical use for moderate and severe psoriasis. Biologics are highly effective in the patients who are not responding to non-biological systems [9].

During the treatment with biologics, it is essential to implement appropriate safety screening and monitoring measures. Further, validated measures of treatment outcome such as psoriasis area and severity index (PASI) and dermatology life quality index should be recorded at appropriate intervals to provide evidence of effectiveness and justification for the continuation of therapy. The measurement should be done at baseline and at 10-16 weeks, depending on the intervention.

At present, there are five biological agents licensed for the treatment of psoriasis vulgaris which are as follows [10].
1. Infliximab, a chimeric human-immune antibody to tumor necrosis factors (TNF-α)
2. Adalimumab, a fully human recombinant antibody to TNF-α
3. Ustekinumab, a fully human recombinant antibody to the p40 component of IL-12/IL-23
4. Etanercept, a fully human soluble p75 TNF-α receptor fusion protein
5. Alefacept, a fusion protein of lymphocyte function associated antigen-3 and immunoglobulin G (IgG) that inhibits T-cell activation.

Biological agents are now routinely used when one or more traditional systemic agents fail to produce an adequate response, or not tolerated because of adverse effects, or are unsuitable due to the presence of comorbidities.

**BIOLOGICAL AGENTS (BIOLOGICS)**

The choice of treatment is influenced by short-term as well as long-term considerations, including the severity of the disease, the effectiveness of a given medication and its side effects, the patient’s quality of life, and the ease of treatment.

Rapidly expanding range of biological agents provide a novel approach in the field of treatment for psoriasis. These are proteins (usually antibodies) with highly specific actions. Severe forms of psoriasis such as erythrodermic and generalized pustular psoriasis can be life-threatening and may require urgent treatment in hospital [11].

As described earlier mainly five biologics are used for the treatment of extensive (moderate to severe) form of psoriasis which is as follows.

**Infliximab**

Infliximab is a chimeric human-murine monoclonal antibody. It is an anti-TNF-α chimeric monoclonal IgG1 antibody. It blocks soluble TNF-α and is also capable of binding transmembrane TNF-α receptor, resulting in complement fixation and antibody-mediated cytolsis. Infliximab is administered via intravenous infusion over a period of 2 hrs. A standard induction dose of 5 mg/kg or 10 mg/kg at week 0, 2, and 6 is followed by repeat single infusion at 8-12 week intervals. It is indicated in a clinical condition requiring rapid disease control, e.g., in unstable erythrodermic or pustular psoriasis due to its very rapid onset of action and high response rate [12-14].

**Adalimumab**

Adalimumab (humira) is a recombinant, fully human monoclonal antibody expressed in Chinese hamster ovary cells (or fully human monoclonal IgG1 antibody against TNF-α). It inhibits (by binding) the p55 and p75 tm TNF receptors but does not bind or inactivate TNF-β. The recommended dosing for adalimumab in psoriasis is 40 mg SC at every 2 weeks. Adalimumab is approved for the treatment of chronic, moderate to severe plaque psoriasis [15,16].

**Etanercept**

Etanercept is a human recombinant fusion protein comprising of the human TNF-α p75 receptor and the Fc portion of human IgG1 antibody, fused together. In contrast to other anti-TNF-α agents which bind to soluble and transmembrane TNF-α, etanercept binds to soluble TNF-α and TNF-β (lymphotoxin-α), both of which are involved in granuloma formation [17].

Etanercept therapy may be initiated S/C at either 50 mg or 25 mg twice weekly followed by 50 mg S/C per week and disease response assessed at 3-4 months. Etanercept should be discontinued if patients do not reach a PASI 50 response by week 12. The most common adverse effects reported are injection site reactions (14%), allergic reactions, headache, and upper respiratory tract infection [18,19].

**Alefacept**

Alefacept is a recombinant fusion protein that combines the first extracellular domain of leukocyte function-associated antigen-3 with the CH1 and CH2 domains of human IgG1 [20]. It inhibits the proliferation and activation of memory T lymphocytes through blockage of LFA-3 interaction and also induces apoptosis of T lymphocytes through mediation between T lymphocytes and NK cells [21].

CD4 counts recommended to be monitored weekly during alefacept therapy due to its effect on T-cells [22]. Alefacept is recommended at every week for 12 weeks in a dose of 15 mg via intramuscular injections, followed by a 12-week drug-free interval, resumed by another 12-week course if CD4 counts remain above 250/µl. If CD4 counts drop below 250/µl for 1 month, alefacept is to be discontinued. If the CD4 count remains <250 cells/µl for 4 continuous weeks, then alefacept treatment must be permanently discontinued. The most common side effects include a headache, nasopharyngitis, influenza, upper respiratory tract infection, liver injury, and pruritus [17,23].

**Ustekinumab**

Ustekinumab is a fully human IgG1k monoclonal antibody with high affinity and specificity for the common p40 subunit shared by IL-12 and IL-23. It finally targets Th1 and Th17 arms of immunity since these are well known to play an essential role in the pathogenesis of psoriasis [15].

It is recommended in moderate to severe psoriasis in a dose of 45 mg 4 weekly (monthly) in the patients weighing <100 kg and 90 mg 4 weekly in the patients weighing more than 100 kg. It is administered as a subcutaneous injection. Efficacy should be assessed at 12-week intervals most probably by PASI score [24,25].

Common adverse effects of biologics include administration site reactions (and acute infusion reactions for infliximab), serious infections, including tuberculosis (extra-pulmonary or miliary), sepsis, and other opportunistic infections have been reported with use of these agents.

Among the TNF-α antagonists, adalimumab, etanercept, and infliximab have longer safety records and experience, and therefore, may be preferable over golimumab (approved for PsA only) or ustekinumab, which is more efficacious than etanercept but lacks long-term experience and safety data.

Choice for the first use of TNF-α antagonist should be based on clinical need and requires a careful assessment of risks and benefits of each agent in the context of the individual patient. For stable disease, particularly if not too severe (e.g., PASI >10 but <20), etanercept or adalimumab is often first options and also in the patients requiring rapid disease control due to early onset of action for these drugs. For patients with unstable or generalized pustular psoriasis, few evidences indicate that infliximab is effective and may be considered first choice amongst the biologics. If the patients not respond to a particular TNF-α antagonist (either primary or secondary failure), a second TNF-α antagonist may be considered [26,27].

Despite the introduction of these current and future biologic agents, topical medications, phototherapy, photochemotherapy, and traditional systemic drugs continue to play an essential role in the therapeutic field of psoriasis. Topical therapies are the mainstay for mild disease either as monotherapy or in combination and are also commonly used in conjunction with phototherapy, traditional systemic agents, or biologic agents for moderate to severe disease [28].

**CONCLUSIONS**

Current treatment strategies require the therapies targeted to the immune system since altered immunity (auto-immunity) is the mainstay in the pathogenesis of psoriasis. Currently, available biologics for psoriasis are target either the T-cells or antigen presenting cells or block the inflammatory action of TNF-α. The increased understanding of the immunopathology of psoriasis and development of biotechnology has led to the rapid development of these engineered proteins (biologics) not only in dermatology but also in rheumatology, gastroenterology, and transplantation medicine.
Biologics appear to offer great promise in the day to day and longer-term management of patients with psoriasis. They appear to offer a safe and effective alternative to conventional systemic therapies and phototherapy for the treatment of moderate to severe chronic plaque psoriasis. Biologics are effective in the treatment of several dermatologic disorders due to their selectivity in targeting specific pathways in the inflammatory cascade of psoriasis. Despite the limitation of their cost, their unique mechanism of action has definitely provided a new ray of hope in the management of psoriasis.

REFERENCES