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# Biologicals in the treatment of psoriasis: The Indian perspective

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## Abstract:

Psoriasis is a common inflammatory skin disorder characterized by itchy erythematous papules and plaques topped with silvery white scales. It has a chronic relapsing course and is associated with significant morbidity and reduction in the quality of life. Therapy of psoriasis is challenging. Topical therapy forms the first line of treatment for stable plaque psoriasis affecting a limited body surface area and in extensive disease systemic agents are indicated. All these drugs have inherent side effects, and none bring prolonged remission of the disease. The other therapeutic modality for psoriasis is phototherapy, but it is delivered through a specialized machine which can be available only at referral centers. Biologics have revolutionized the management of psoriasis as they can bring a remission of disease up to several years. Although limited availability and high cost prohibit their regular usage, Indian dermatologists are rapidly adopting biologics in the treatment of psoriasis.

## Keywords:

Biologics, psoriasis, secukinumab

Psoriasis is a common inflammatory skin disorder characterized by itchy erythematous papules and plaques topped with silvery white scales. It may affect any body part including scalp and nails. It may affect the skeletal system in the form of “psoriatic arthropathy,” which may or may not coexist with skin lesions. About 2%–3% of the world’s population is affected by the disease.<sup>[1]</sup> It has a chronic relapsing course and persists for the lifetime of an affected individual. Hence, it is associated with significant morbidity and reduction in the quality of life in terms of personal and social interaction.

Therapy of psoriasis is challenging. Whatever therapeutic modality may be used, the disease may go for remission but relapses at regular intervals (seasonal exacerbation) or otherwise. Till few years back, there was no treatment for psoriasis which prolongs the duration of remission in these patients.

Topical therapy forms the first line of treatment for stable plaque psoriasis affecting a limited body surface area (BSA). In patients with extensive disease systemic agents are indicated. Methotrexate is the most commonly used systemic agent because of its proven efficacy and affordability but is associated with systemic toxicity on prolonged usage. Other common systemic drugs used in psoriasis are acitretin and cyclosporine-A. Systemic retinoids are contraindicated in females of reproductive age-group, and cyclosporine-A are indicated in specific clinical situations. All these drugs have inherent side effects and none bring prolonged remission of the disease.

The other therapeutic modality for psoriasis is phototherapy and photochemotherapy. Photochemotherapy is a therapeutic method in which psoralens are used in combination with ultraviolet-A (UVA). Psoralens are compounds that sensitize cells to the effects of UVA light. Depending on the source of UVA, it can be psoralen + UVA (PUVA) (artificial phototherapy unit) or PUVA sol (sunlight).

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PUVA therapy requires a UVA machine and can only be administered at higher centers whereas in PUVAsol the dose of UVA cannot be adjusted accurately. The current phototherapeutic modality for widespread psoriasis is narrow-band ultraviolet-B (NB-UVB) therapy. The main advantage of NB-UVB phototherapy is that it is free of the adverse effects associated with systemic drugs. However, this therapy can be delivered through a specialized machine which can be available only at referral centers.

Biologics have been introduced in the therapy of psoriasis in the past decade. The introduction of biologics has revolutionized the management of psoriasis, and new molecules are continually being added to this group. Biologics target specific points in the inflammatory pathway without interacting with other proteins hence they are associated with fewer systemic adverse effects. These are considered unique in the treatment of psoriasis as longer remission period can be expected. In developing countries like India, cost of these therapeutic agents is the prohibitive factor for regular usage. However, Indian dermatologists are rapidly adopting biologics in the treatment of psoriasis.

In the following section role of biologics in the therapy of psoriasis will be discussed.

## Biologics and Biosimilars

US Food and Drug Administration defines “biologic” as an agent derived from living material (human, plant, animal, or microorganism) used for the prevention, treatment or cure of disease in humans.<sup>[2]</sup> In general, it refers to protein molecules therapeutically used to target specific points of the immunological processes. Biosimilars are biological products designed to be highly similar to the reference innovator drug.<sup>[3]</sup> Their efficacy and safety profile is similar to the reference molecule. The emergence of biologics has brought about a significant progress in the management of psoriasis. Herein, we briefly discuss the indications, various types, and adverse effects associated with the biologics used for the treatment of psoriasis in general.

## Indications for Biologic Therapy in Psoriasis

Biologics are indicated in patients who fulfill the eligibility criteria as given below. However, a thorough assessment of the patient regarding risks and benefits should be made before administering the biologic.

Eligibility criteria:<sup>[4]</sup> Patient must have severe disease as defined in (a) and fulfill one of the clinical categories listed in (b).

(a) Severe disease defined as a “psoriasis area severity index (PASI)” score of 10 or more

(or a BSA of 10% or greater where PASI is not applicable) and “dermatological life quality index” >10. In exceptional circumstances, patients with severe disease may fall outside this definition but should be considered for treatment (disease affecting high-impact sites such as genitalia, hands, feet, head, and neck with associated significant functional or psychological morbidity)

- (b) Fulfill at least one of the following clinical categories
- Where phototherapy\* and alternative standard systemic therapy† are contraindicated or cannot be used due to the development or risk of important treatment-related toxicity
  - Are intolerant to standard systemic therapy
  - Are unresponsive to standard systemic therapy
  - Have significant coexistent comorbidity which precludes use of systemic agents
  - Have severe, unstable, life-threatening disease.

\*Phototherapy may be inappropriate in patients:

- Who have exceeded safe exposure limits (150–200 treatments for PUVA, 350 treatments for NB-UVB)
- Who are nonresponsive or relapse rapidly
- Who have a history of skin cancer or repeated episodes of severe sunburn
- Who are intolerant of UV exposure, especially if skin phototype I (sun-sensitive)
- For logistical reasons.

†Standard systemic therapy includes cyclosporine (2.5 mg/kg daily; up to 5 mg/kg daily), and in men and women not at risk of pregnancy, methotrexate (single dose [oral, subcutaneous, intramuscular] 15 mg weekly; maximum 25 mg weekly) and acitretin (25–50 mg daily).

## Pretreatment Assessment

Before administering any biologic the following investigations should be carried out:<sup>[4]</sup>

- Complete hemogram (CH)
- Renal function tests, urine analysis
- Liver function tests (LFTs)
- Mantoux test/interferon-gamma release assay (IGRA), chest X-ray and high-resolution computerized tomographic scan (if indicated)
- Screening for viral infections hepatitis B (hepatitis B virus surface antigen), hepatitis C (anti-HCV antibody), human immunodeficiency virus (HIV 1 and 2)
- Electrocardiogram and echocardiography (if indicated).

## Monitoring While on Therapy with Biologics

- Periodic history and physical examination

- Yearly Mantoux test/IGRA and periodic CH and LFT.

### Indications for Stopping Therapy

- Failure to achieve an adequate response following treatment initiation or when treatment response is not maintained
- A serious adverse event such as malignancy (excluding nonmelanoma skin cancer), severe drug-related toxicity, and severe intercurrent infection (temporary withdrawal)
- Pregnancy (temporary withdrawal)
- Elective surgical procedures.

### Biologics Used in Psoriasis

Various biologics currently used in the treatment of psoriasis have been listed in Table 1. The biologics and biosimilars which are currently available in India will be discussed in this article.

#### Tumor necrosis factor alpha inhibitors

Tumor necrosis factor (TNF) is a proinflammatory cytokine which plays an important role in the pathogenesis of psoriasis. It exists in two forms, soluble TNF (sTNF) and cell surface bound precursor transmembrane TNF (tmTNF) both of which are biologically active. They bind to either of the two TNF receptors leading to nuclear factor-kappa B activation and promote inflammation and/or apoptosis. In addition, tmTNF itself can act as a ligand to induce cell activation, cytokine suppression, or apoptosis of the tmTNF bearing cell through a reverse signaling process.<sup>[4]</sup>

There are currently two approved groups of biologic agents that target TNF: anti-TNF monoclonal antibodies (infliximab and adalimumab), and sTNF receptors (etanercept). All three agents specifically bind both soluble and transmembrane forms of TNF and act by:

- (i) Blocking TNF receptor-mediated mechanisms, and
- (ii) Inducing tmTNF mediated reverse signaling processes.<sup>[5]</sup> The dosing schedules of TNF- $\alpha$  inhibitors in psoriasis are summarized in Table 2.<sup>[4]</sup>

TNF- $\alpha$  inhibitors are generally considered safe and cause nonlife-threatening adverse effects, but occasionally they may be severe. The adverse effects caused by TNF- $\alpha$  inhibitors are listed in Table 3.<sup>[4]</sup>

#### Contraindications for tumor necrosis factor- $\alpha$ inhibitors

Absolute

- Untreated tuberculosis
- Active infections (including infected prosthesis,

**Table 1: Biologics currently used in the treatment of psoriasis**

Type of biologic	Drugs
TNF- $\alpha$ inhibitors	Infliximab*, adalimumab*, etanercept*, golimumab <sup>†</sup> , certolizumab <sup>†</sup>
Anti-IL 12/23 antibody	Ustekinumab
Anti-CD6 antibody	Itolizumab*
IL-17A inhibitors	Secukinumab*, ixekizumab
IL-17RA inhibitor	Brodalumab

\*Biologics available in India; <sup>†</sup>FDA approved for psoriatic arthritis. TNF- $\alpha$ =Tumor necrosis factor alpha, IL=Interleukin, IL-17RA=IL-17 receptor A, FDA=Food and Drug Administration

**Table 2: Dosing schedules of tumor necrosis factor alpha inhibitors in psoriasis**

Drug	Dosage schedule	Assessment of response
Infliximab	Adults: 5 mg/kg 1 at weeks 0, 2, 6 and then every 8 weeks (intravenous)	14 weeks
Adalimumab	Adults: 80 mg week 0, 40 mg week 1, then every other week (subcutaneous)	16 weeks
Etanercept	Adults: 25 mg biweekly (50 mg once weekly up to 24 weeks); or 50 mg twice weekly up to 12 weeks reduced to once weekly thereafter (subcutaneous) Children >8 years: 0.8 mg/kg up to maximum 50 mg weekly (subcutaneous)	12 weeks

severe sepsis)

- History of recurrent or chronic infections
- Congestive cardiac failure (New York Heart Association grade III or IV)
- Multiple sclerosis or optic neuritis
- Malignancy or premalignancy states excluding:
  - Adequately treated nonmelanoma skin cancer
  - Malignancies diagnosed and treated more than 5 years previously (where the probability of total cure is very high).
- Pregnancy and lactation.

Relative

- HIV infection
- Hepatitis B and C virus infection.

#### Anti-CD6 antibody

Itolizumab is a humanized IgG1 monoclonal antibody developed in India (Alzumab, Biocon Limited, Bangalore, India).<sup>[6]</sup> It is approved in India and Cuba for the treatment of moderate to severe plaque psoriasis.<sup>[7]</sup> Itolizumab selectively binds to CD6, a pan-T-cell marker causing downregulation of priming and activation of T-cells leading to reduction in synthesis of pro-inflammatory cytokines and chemokines.<sup>[4]</sup>

#### Itolizumab dosing schedule

Recommended dose of itolizumab for the treatment of plaque psoriasis is 1.6 mg/kg given as intravenous

**Table 3: Adverse effects caused by tumor necrosis factor alpha inhibitors**

Adverse effects	Etanercept	Infliximab	Adalimumab
Common	Injection site reactions pruritus, URTI	Acute infusion reaction (fever, chills, nausea) headache, pruritus, urticaria, elevated transaminases, URTI	Injection site reactions, headache, URTI
Uncommon but severe	Severe infections, opportunistic infections, reactivation of latent TB or progression of recently acquired TB, new onset or exacerbation of CNS demyelinating disorders (e.g., MS), possible increased risk of malignancy (lymphoma), drug-induced lupus, exacerbation of CCF, vasculitis, aplastic anemia	Same as for etanercept, pancytopenia	Same as for etanercept

URTIs=Upper respiratory tract infections, TB=Tuberculosis, CNS=Central nervous system, MS=Multiple sclerosis, CCF=Congestive cardiac failure

infusion once every 2 weeks for 12 weeks, followed by 1.6 mg/kg every 4 weeks up to 24 weeks.<sup>[6]</sup>

#### Adverse effects

Infusion reactions, infections and rarely exfoliative dermatitis, erythrodermic psoriasis, adjustment disorder with anxiety and bacterial arthritis.<sup>[6]</sup>

#### Contraindications

Inflammatory diseases and systemic autoimmunity (other than psoriasis), psoriatic erythroderma, psoriatic crisis, and any active serious infection.<sup>[5,6]</sup>

#### Interleukin-17A inhibitors

Secukinumab is a recombinant, fully human antibody that selectively binds and neutralizes interleukin (IL)-17A. IL-17A is the primary effector of type 17 helper T (Th17) cells, however, in psoriatic lesions, it is secreted by other cells such as  $\gamma\delta$  T-cells, neutrophils, and possibly mast cells also.<sup>[5]</sup> IL-17A acts as the master cytokine in the pathogenesis of psoriasis as it stimulates keratinocytes to secrete chemokines and other pro-inflammatory mediators that recruit additional inflammatory cells, including neutrophils, Th17 cells, dendritic cells, and innate lymphoid cells.<sup>[5]</sup> In comparative studies, secukinumab was found to be more effective than etanercept and ustekinumab in clearing the psoriatic lesions and improving the patients' quality of life.<sup>[8]</sup>

#### Secukinumab dosing schedule

Recommended dosage is 300 mg (subcutaneous injection) at weeks 0, 1, 2, 3, and 4 followed by 300 mg every 4 weeks. For some patients, a dose of 150 mg may be acceptable.<sup>[5]</sup>

#### Adverse effects

Nasopharyngitis, diarrhea, upper respiratory tract infection, inflammatory bowel disease, and increased risk of candida infection.<sup>[5]</sup>

#### Contraindications

Previous serious hypersensitivity reaction to secukinumab or to any of the excipients, chronic or a

history of recurrent infection and inflammatory bowel disease.<sup>[5]</sup>

Ixekizumab is a humanized monoclonal antibody indicated for the treatment of adults with moderate to severe plaque psoriasis. It also acts by inhibiting IL-17A like secukinumab. It is administered at a dose of 160 mg (two 80 mg injections) at week 0, followed by 80 mg at weeks 2, 4, 6, 8, 10, and 12, then 80 mg every 4 weeks subcutaneously.<sup>[9]</sup> Adverse effects and contraindication are similar to secukinumab.

#### Anti-interleukin 12/23 antibody

Ustekinumab is a fully human monoclonal antibody that binds the shared p40 subunit of IL-12 and IL-23.<sup>[10]</sup> These cytokines are secreted by antigen-presenting cells and are important mediators of the differentiation of naive T-cells into Th1 and Th17 cells. It also inhibits IL-12-and IL-23-induced IFN- $\gamma$ , IL-17A, TNF- $\alpha$ , IL-2, and IL-10 secretion.<sup>[10]</sup> It is administered based on weight at 45 mg ( $\leq 100$  kg) or 90 mg ( $>100$  kg) by subcutaneous injection at weeks 0 and 4, then every 12 weeks thereafter.<sup>[10]</sup> Injection site reaction, headache, nasopharyngitis, and upper respiratory tract infections are the most common adverse effects associated with ustekinumab.<sup>[10]</sup> Ustekinumab is currently not available in India.

#### Interleukin-17RA inhibitor

Brodalumab is a fully human monoclonal antibody which targets the IL-17 receptor A (IL-17RA). It inhibits binding of IL-17A and IL-17F to the IL-17RA. Recommended dosage is 210 mg by subcutaneous injection at weeks 0, 1, and 2 followed by 210 mg every 2 weeks.<sup>[11]</sup> Arthralgia, headache, fatigue, diarrhea, oropharyngeal pain, myalgia, injection site reactions, influenza, neutropenia, and tinea infections are the most common reported adverse effects. It is contraindicated in patients with chronic or history of recurrent infections and Crohn's disease.<sup>[11]</sup>

## Conclusion

Biologics represent the future of therapeutics in psoriasis. This group of therapeutic agents induces long-term

remission in long-standing psoriatic patients. These are the drugs of choice in systemic therapy-resistant cases of psoriasis or patients who have developed significant side effects related to long-term anti-psoriatic therapy. Psoriatic arthritis, an incapacitating disease in some patients responds miraculously to these agents. Secukinumab is the latest agent in the biologic therapy of psoriasis. It is relatively safer as compared to earlier biologics and may bring a remission of disease up to several years.

In a resource poor country like India limited availability, high cost and no insurance coverage for the use of these agents are the constraints for their utilization. These drugs have been in wide use in large cohorts of white-skinned patients in various western countries. However, Indian data on the use of biologics in psoriasis are sparse, available from the premier institutions and metropolitan cities. Large-scale and long-term data on the use of biologics among patients with psoriasis in India may be available in future so that its safety among brown-skinned individuals can be determined.

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### Conflicts of interest

There are no conflicts of interest.

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