

REVIEW

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## Biological Treatment of Psoriasis

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**Abstract:** Psoriasis is a common, chronic, inflammatory disease affecting millions of people around the world. Presented in the first 5 parts of the American Academy of Dermatology Psoriasis Guidelines of Care is evidence supporting the use of topical treatments, phototherapy, traditional systemic agents, and biological therapies for patients with psoriasis.

Biological therapy is a new, safe, and effective treatment for moderate to severe psoriasis. This type of medication is designed to target specific components of the immune system. There is a need to review the recommended treatment guidelines for psoriasis because the perception and demands of patients are constantly changing. In future, this class of drugs will expand as new biologics are being developed. In this review, we emphasize the description of psoriasis and therapy scheme for mild to severe forms and options (classification according to the manifestation of the disease or to the application form) for biological treatment.

**Keywords:** psoriasis, biological treatment, application form, manifestation

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## Introduction

Psoriasis is a chronic skin disease causing scaling and inflammation with or without itching. Psoriasis is one of the world's most common skin diseases affecting 2% to 3% of the population. An abnormality in the immune system fighting infection and allergic reactions can be caused by psoriasis. Due to the fact that up to 40% of patients have family members with the same problem, genetic factors could be involved.<sup>1</sup>

There are several types of psoriasis including (1) plaque psoriasis, which consists of rounded or oval plaques of affected skin that are usually red and covered with a silvery scale. The plaques generally outgrow slowly and appear on the elbows, knees, scalp, or near the buttocks. (2) Inverse psoriasis is also a plaque type of psoriasis, but its surface is usually moist. Inverse psoriasis is the opposite of typical psoriasis plaques. It tends to affect skin creases, especially in the underarm, groin, buttocks, or genital areas or under the breast. (3) Pustular psoriasis is where the skin plaques are studded with pimples or pustules. (4) Guttate psoriasis consists of many dime-sized or smaller red squamate plaques that grow suddenly and simultaneously. This type of psoriasis often occurs in a young person who has strep throat or a viral upper respiratory infection.<sup>1-3</sup>

Psoriasis treatment selections are numerous (Table 1) and cover over-the-counter medications, topical prescription, phototherapy, systemic therapies, and biologics. Traditional topical treatments comprise

tars, corticosteroids of varying potency, vitamin D and vitamin A analogs, and anthralin. Methotrexate and cyclosporine are known as the traditional systemic treatments. They are used for severe psoriasis resistant to other medications because they have potential side effects. Despite the numerous treatment modalities that are available, many psoriasis patients are displeased with their treatment results. Most people with psoriasis believe that they are undertreated and desire better disease control.<sup>1-4</sup>

Chronic psoriasis is an immune mediated, inflammatory skin condition affecting approximately 2% of the general population. Psoriasis commonly occurs before the age of 35 and is a lifelong disease with a heavy burden on quality of life of patients. From 10% to 30% of patients suffer concomitantly from psoriatic arthritis (PsA), and many patients have other comorbid disorders, including obesity, diabetes, dyslipidemia, hypertension, and an increased rate of cardiovascular disease. Conventional systemic treatment with methotrexate, cyclosporine, and acitretin may be connected with relevant side effects and organ toxicity that preclude long-term therapy. Clarification of the immunopathogenesis of psoriasis has led to the emergence of new therapies targeting the immune cells and molecules that stimulate and keep the psoriatic lesions. Biological agents are commonly proteins derived from recombinant DNA technology, hybridomas, blood, and human cells. These agents are designed to specifically interfere with

**Table 1.** The schematic form of abstract.

Application form				Manifestation			
Topical	Systemic	Novel biologics	Other agents	Mild	Mild to moderate	Moderate	Severe
1-Corticosteroids 2-Calcineurin inhibitors	Biological treatment a-TNF- $\alpha$ inhibitors – <i>Etanercept</i> – <i>Infliximab</i> – <i>Adalimumab</i>  b-P40 IL12/23 inhibitor – <i>Ustekinumab</i>  c-T-cell agents – <i>Alefacept</i> – <i>Efalizumab</i>	1-Anti-IL-23  2-Anti-IL-17 agents  3-Anti-TNF agents	1-PDE inhibitors 2-Kinase inhibitors  3-Lipids 4-Kangal fishes	1-Topical agents 2-Cortico steroids  3-Calcineurin inhibitors	Phototherapy Immunosuppressive agents –	Immunosuppressive agents	Biologics



T cell activation and functions or with cytokines in psoriasis. The release of TNF- $\alpha$  and TNF- $\alpha$ -bearing cells appear to be critical for both psoriasis and PsA. The anti-TNF- $\alpha$  agents effectively relieve signs and symptoms of PsA and prevent radiographic disease progression. These agents are efalizumab, etanercept, infliximab, and adalimumab.<sup>1,5,6</sup>

The pathogenesis of psoriasis has led to the development and utilization in the past 5 years of new drugs with potentially fewer side effects. These agents are custom-made protein molecules set up specifically targeting a particular cell type or cytokine that covered the pathogenesis of psoriasis. The scientists hope that these new biologic agents will not cause side effects in other organs such as the bone marrow, liver, and kidney. So the use of systemic agents is supported for moderate-to-severe psoriasis among dermatologists.<sup>3-5</sup>

### Topical corticosteroids

Topical corticosteroids suppress epidermal inflammation in keratinocytes and fibroblasts. Topical corticosteroids influence cytokine synthesis, for example, IL-1 $\alpha$  and IL-6 and cell proliferation of keratinocytes and fibroblasts. The production of IL-1 $\alpha$  and IL-6 increases the proinflammatory stimuli like TBN- $\alpha$ , which inactivates the inhibitory transcription factor I kappaB $\alpha$ . Thus, the transcription factor NF $\kappa$ B is released, which induces cytokine gene expression. The transcription of cytokine genes is inhibited by corticosteroids.<sup>7,8</sup>

### Calcineurin inhibitors

The calcineurin inhibitors pimecrolimus and tacrolimus are used as topical drugs. They bind and inactivate calcineurin, a calcium- and calmodulin-dependent serine and threonine phosphatase. This leads to inhibition of activation of T-lymphocytes, downregulating of several interleukins, interferon-gamma, granulocyte-macrophage colony stimulating factor, and tumor necrosis factor. Furthermore, they affect the function of mast cells, basophils, and Langerhans cells. These mediators are involved in the pathogenesis of inflammatory skin disorders like psoriasis. Pimecrolimus does not step in the differentiation, maturation, and function of cells like dendritic cells/Langerhans cells, which are involved in immunosurveillance.<sup>9-11</sup>

### Novel biologics

Many of the medications in clinical trials for psoriasis are currently biologics, including soluble receptor proteins, fully human or humanized antibodies, or occasionally antibody fragments. Biologics are administered intravenously, intramuscularly, or subcutaneously. There are currently 9 different biologics undergoing investigation for the treatment of psoriasis. Examples of these biologics are anti-IL-23 and anti-IL-17.

#### Anti-IL-23

Three anti-IL-23 agents are in development. Briakinumab (ABT874) is a fully human monoclonal antibody that targets the p40 subunit of IL-12 and IL-23 in a similar manner to ustekinumab. In a phase III trial, briakinumab was compared with etanercept and methotrexate, resulting in reduction of clinical severity as measured by the Psoriasis Area Severity Index (PASI) and score (PASI-75). Because of an increased incidence of major cardiovascular events, the drug manufacturers withdraw the application for approval of briakinumab by the US Food and Drug Administration. Furthermore, APG2305 is a novel orally administered drug that consists of a short sequence of peptides that inhibit the IL-23 receptor. This medication is also currently undergoing phase II trials.<sup>12-14</sup>

#### Anti-IL-17 agents

IL-17 is manufactured by both the innate and adaptive immune system cells including neutrophils, mast cells, and CD8 (Tc17) and CD4 (Th17) T cells. There are 2 isoforms of IL-17, which are IL-17A and IL-17F. These isoforms are expressed by T cells. Secukinumab, LY2439821 and Fezakinumab (ILV-094) are the samples of cytokines, and these 3 cytokines are similar in function and signal through the same IL-17 receptor complex. Secukinumab (AIN457) is a fully human antibody against IL-17A. In a phase II trial, 36 patients with psoriasis receiving a single infusion of secukinumab at 3 mg/kg were studied, and the mean PASI score was reduced. LY2439821 is another biologic and humanized anti-IL-17A antibody that is in phase II trials for psoriasis. AMG827 is a fully human antibody that blocks the IL-17 receptor and, therefore, inhibits all 3 isoforms of IL-17A/F. In addition, Fezakinumab (ILV-094) is an IL-22-specific monoclonal antibody undergoing early trials in psoriasis.<sup>15-17</sup>



## Anti-tumor necrosis factor (Anti-TNF) agents

Three anti-TNF agents are already available for clinical use in psoriasis: etanercept, infliximab, and adalimumab (a fourth, golimumab, is only marketed for psoriatic arthritis). An additional inhibitor of TNF- $\alpha$ , certolizumab pegol, is currently in phase II trials. It is a humanized monoclonal antibody fragment and binds to a polyethylene glycol moiety to increase its half-life. As a result, it doesn't affect apoptosis of inflammatory cells that occurs with other anti-TNF agents. Given below are details about the anti-TNF agents, etanercept, infliximab, adalimumab, and ustekinumab.

### Etanercept

Etanercept is a biopharmaceutical drug for treating autoimmune diseases. It interferes with the "master regulator" of the inflammatory response by inhibiting TNF and fuses the TNF receptor with the constant end of the IgG1 antibody.

Etanercept works as a decoy receptor by binding to TNF. TNF  $\alpha$  is a cytokine produced by the 2 types of white blood cells: lymphocytes and macrophages. Etanercept increases the transport of white blood cells to the sites of inflammation and stimulates the immune response, thus decreasing inflammation through additional molecular mechanisms. Two types of TNF receptors are known: soluble TNF receptors, which are used to deactivate TNF and weaken the immune response, and TNF receptors, which are embedded in white blood cells that respond to TNF by releasing other cytokines.

TNF receptors are located on the surface of all nucleated cells, which is why they cannot be found in the un-nucleated red blood cells. Etanercept simulates the inhibitory effects of soluble TNF receptors with the difference of having a more long-lasting biologic effect due to its fusion protein characteristics.<sup>18–20</sup>

### Infliximab

The monoclonal antibody infliximab is used to treat autoimmune diseases and binds to TNF  $\alpha$  and causes programmed cell death of TNF- $\alpha$ -expressing activated T lymphocytes, which play an important role in mediating inflammation. In addition, infliximab binds with high affinity to the soluble, free floating in the blood, and transmembrane forms of TNF- $\alpha$

leading to inhibition of the effective binding of TNF- $\alpha$  with its receptors. Infliximab is capable of neutralizing all forms of TNF- $\alpha$  and lysis cells.<sup>21,22</sup>

Some of the biological activities of infliximab are the induction of proinflammatory cytokines like IL-1 and IL-6, enhancement of leukocyte movement or migration from the blood vessels into the tissues by increasing the permeability of endothelial layer of blood vessels, and increasing the release of adhesion molecules.<sup>23</sup>

### Adalimumab

Adalimumab is a human monoclonal antibody, in contrast to the mouse-human chimeric antibody infliximab and the TNF receptor-IgG fusion protein etanercept. Adalimumab, used as subcutaneous injection, binds to TNF  $\alpha$  and inactivates it, leading to downregulating the inflammatory reactions.<sup>24,25</sup>

### Ustekinumab

The human monoclonal antibody ustekinumab is directed against interleukin (IL)-12 and IL-23. These ILs are naturally occurring proteins that regulate the immune system by activating certain T-cells.<sup>26</sup>

### Other agents

An agent targeting P-selectin glycoprotein ligand-1 is under development for psoriasis. P-selectin glycoprotein ligand-1 is expressed on the surface of activated T cells. It mediates entry of T cells into inflamed tissues and by binding with P-selectin on endothelial cells.<sup>23</sup>

### Efalizumab

Efalizumab binds to the subunit of lymphocyte function-associated antigen 1 and acts as an immunosuppressant by inhibiting lymphocyte activation and cell migration out of blood vessels into tissue. Efalizumab was withdrawn from the market in 2009 because of association with brain infections.<sup>23</sup>

### Alefacept

Alefacept (Amevive) was the first approved (2003) biologic for the treatment of psoriasis. Alefacept was withdrawn in 2011. Alefacept is a recombinant dimeric fusion protein that inhibits the growth of some T cell types. The mode of action of alefacept involves a dual mechanism. On the one hand, alefacept interferes with CD2 on the T cell membrane leading to



inhibition of the costimulatory molecule lymphocyte function-associated antigen (LFA)-3/CD2 interaction and the activation of CD4<sup>+</sup> and CD8<sup>+</sup> cells.<sup>27</sup> On the other hand, alefacept induces apoptosis of memory-effector T lymphocytes, giving rise to an enhanced binding between natural killer cells and T cells. The typical psoriatic symptoms are the results of proliferated keratinocytes, which in turn are stimulated by T cells. Alefacept prohibits these reactions, leading to a clinical improvement of psoriasis.<sup>28</sup>

### Phosphodiesterase inhibitors

Apremilast is the phosphodiesterase (PDE)-4-inhibitor and is currently used in phase III trials. PDE-4-inhibitors limit T-cell secretion of proinflammatory cytokines like TNF-alpha and IFN-gamma.<sup>29</sup> PDE-4 plays a key role in degrading cyclic adenosine monophosphate (cAMP) in cells.<sup>30</sup>

### Kinase inhibitors

The protein kinase C (PKC) family contains 10 isoenzymes.<sup>31</sup> These are important for several signal transduction cascades. Sotrastaurin is inhibitor of the 3 isoform PKCs such as PKC-alpha, PKC-beta, and PKC-theta<sup>32</sup> and effects more than 200 kinases. These 3 isoforms are important for T-cell signaling<sup>33</sup> and critical for generation of IFN-gamma and IL-17.<sup>34</sup>

The molecules connecting with several cytokine receptors to the signal-transducer and activator of transcription pathways are the Janus kinases, (JAK) JAK1-3 and TYK2.<sup>35</sup> JAK1-2 plays significant role in IFN signaling and JAK3 transducer signals from IL-2, IL-7, IL-15, and IL-21.<sup>36,37</sup> The 3 drugs of this class are CP-690550, ASP015K, and INCB28050, which are inhibiting JAK1 and JAK3, JAK3 and INCB28050, JAK1 and JAK2, respectively, in development.

Cytoplasmic tyrosine kinases like spleen tyrosin kinase transduces signal critical for T-cell, macrophage, neutrophil, and mast cell function.<sup>38</sup> Fostatinib as prodrug is currently undergoing phase II trials in psoriasis and quickly converts after its absorption.<sup>39</sup>

Mitogen-activated protein kinases are substantial for many inflammatory diseases,<sup>40</sup> but p38 mitogen-activated protein kinase shows a critical role in regulating the biosynthesis of many inflammatory cytokines like TNF-alpha<sup>41,42</sup> BMS 582949 is the highly selective p38 mitogen-activated protein kinase

inhibitor and is used in a phase II clinical trial for psoriasis.<sup>42</sup>

Five of the 7 members of the epidermal growth factor family are upgraded in psoriatic skin because the epidermal growth factor receptor has intrinsic tyrosine kinase activity. There are studies in the literature showing the tyrosine kinase inhibitor erlotinib<sup>43</sup> inhibiting this pathway and its phase II clinical trials.<sup>43-45</sup>

### Lipids

Sphingosine-1-phosphate (S1P) is a lysophospholipid mediating biological effects through the G-protein coupled S1P<sub>1-5</sub> receptors. S1P<sub>1</sub> receptor agonists present a novel approach in the treatment of various autoimmune diseases by hindering the exit of lymphocytes from lymph nodes and other secondary lymphoid organs.<sup>46</sup> The oral S1P agonist ACT128800 is undergoing phase II trials in psoriasis. It is known that oxidized phospholipids promote inflammation.<sup>47-49</sup> The synthetic anti-inflammatory oxidized phospholipid analog VB-201 attenuates inflammation and is currently in a phase II clinical trial in psoriasis.<sup>48</sup>

### Kangal fishes

Another biologic therapy comprises the so-called Kangal fishes, originating in a place named Kangal in the province Sivas and in other regions of Anatolia in Turkey. The main advantages of this fish therapy are the absence of side effects and the long-term improvement effect of psoriasis, which lasts for approximately 9 months. This is especially true of the type Garra Rufa, an example of the type known as the nibbling/noshing fish. These are 10 to 14 cm long and live in water of approximately 35°C. Because of these high temperatures, there is a lack of animal or vegetable nutrition. The fishes are hungry. The anger of the people who are bathing in these waters is an easily accessible protein source for these fishes. The water in Kangal contains potassium, magnesium, hydrocarbonate, sulphate, and the skin-permeable selenium in high concentrations. The water is hypotonic, oligometalic, and has a high pH value. The psoriasis patients must take the bath twice a day for every 3 to 4 hours over a period of at least 3 weeks. There is no proof of what exactly is responsible for the effect of the Kangal fishes. It is assumed that the selenium in the water or the absence of stress could be crucial, without any evidence.



## Future therapies

The use of RNA interference as a drug is one of the possible therapeutic strategies to target the pro-inflammatory cytokines involved in psoriasis, as shown by several phase I and II ongoing clinical trials. On the basis of their role in psoriasis, suitable mRNA targets are TNF-alpha, IL 20, and IL 23. A recent study showed that local small RNA therapy against TNF-alpha provided amelioration in psoriasis in a xenograft transplantation model. These results indicate that RNA interference is a potential therapy in treatment of inflammatory psoriasis disease.<sup>50,51</sup>

International researchers have acknowledged these differences by forming an organization known as GRAPPA (Group for Research and Assessment of Psoriasis and Psoriatic Arthritis). GRAPPA is working to define the tools used in measuring psoriatic arthritis treatment success, including outcome measures and international treatment guidelines. The effort and excitement surrounding psoriatic arthritis research bodes well for the community, leading to encouraging news about treatment options and more accurate assessment scores.

## Conclusion

Biological treatments can be expensive and give insufficient treatment when compare with conventional therapy. Nowadays, clinical experince of biological therapies in psoriasis has some limitations. Although there are no studies assessing the efficacy of biologics, biologics are thought to be safe and effective treatment in mild to moderately severe psoriasis. In addition, these are highly tolerable anti-inflammatories, with fewer side effects, being mild and transient in nature. The combination of biologics with conventional treatments may be of interest to improve efficacy, limit toxicity, and reduce the cost of psoriasis therapy.

## Author Contributions

Conceived and designed the experiments: HYK, EG, YB. Analyzed the data: HYK, EG, YB. Wrote the first draft of the manuscript: HYK, EG, YB. Contributed to the writing of the manuscript: HYK, EG, YB. Agree with manuscript results and conclusions: HYK, EG, YB. Jointly developed the structure and arguments for the paper: HYK, EG, YB. Made critical revisions and approved final version: HYK, EG, YB. All authors reviewed and approved of the final manuscript.

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