Abstract
Psoriasis is a chronic, systemic T-cell mediated autoimmunity skin disease, potentially associated with arthritis. The new understanding of immunopathogenesis and inflammatory cytokine pathways was actually the rationale for developing and introducing biological drugs in the treatment of moderate to severe psoriasis and psoriatic arthritis. Different from the traditional systemic drugs that impact the entire immune system, biologics target only specific points of the immune system. This review focuses on five biologics which target either T-cells (alefacept) or TNF-alpha (etanercept, adalimumab and infliximab) or interleukin IL-12/IL-23 (ustekinumab) – their efficacy, safety, patient monitoring and recommended dosage.

The purpose of the treatment guidelines presented here is to provide a high standard of continuing care of psoriasis and psoriatic arthritis patients.

Key words: psoriasis, immunological aspects, alefacept, etanercept, adalimumab, infliximab, ustekinumab.

Introduction
Current research on the pathophysiology of psoriatic disease has led to the definition shifting from "disease of the skin" to "T-cell mediated disease" [4].

Psoriasis is a genetic, systemic, T-cell mediated, autoimmune disorder. Its genetic component is supported by the fact that several genetic loci called psoriasis susceptibility (PSORS1–PSORS9) are possibly responsible for development of psoriasis [10, 11].

In addition to the genetic predisposition, environmental triggers are also involved in disease onset and exacerbations.

Psoriasis is a chronic/relapsing, potentially debilitating immunoinflammatory, multisystem disease with predominantly skin and joint manifestations, affecting approximately 2% of the general population; rates vary depending on ethnicity and geography [1]. It is characterized by sharply demarcated erythematous plaques with silvery scales affecting the skin and scalp, ranging from a few papules, plaques, to generalization, covering the entire body surface.

Nail changes include subungual hyperkeratosis, onycholysis, pitting and "oil spots". The clinical/morphological spectrum of psoriasis is various, the most common type is chronic plaque psoriasis (85–90%), compared with less common subtypes such as guttate, inverse, pustular or erythrodermic.

Psoriatic arthritis (PsA) occurs in 6–42% of patients with preexisting cutaneous psoriasis, in 10–15% of patients PsA developed before skin manifestations [2]. The great variety of clinical forms of PsA (oligo-articular, polyarticular, distal, mutilans and spondylitis) was encompassed in the definition of Moll and Wright [7]. Recently appeared CASPAR (classification criteria for PsA) criteria are based on: established inflammatory arthritis and additional at least 3 criteria as current psoriasis or psoriasis history, positive family history of psoriasis, dactylitis, juxta-articular new bone formation, rheumatoid factor negativity and nail dystrophy [8, 12].

Other conditions associated with psoriasis, PsA or both include autoimmune diseases such as Crohn’s disease, cardio-metabolic conditions (cardiovascular, diabetes, dyslipidaemia, obesity), depression, lymphomas, which could have great implications in therapeutic strategies.
Comorbidities in psoriatics like psoriasis alone impair the physical health, and psychological well-being, leading to substantial adverse sociological consequences and a significant economic burden [9].

**Immunopathogenesis of psoriasis**

There is evidence of dysregulation of the innate immune system in psoriasis [3, 14], the crucial role being played by the plasmacytoid dendritic cell – the producer of the innate cytokine interferon-α which is actually an inducer of psoriasis [13]. Plasmacytoid dendritic cells are numerically increased and activated in the early psoriatic lesions. Innate immune cells produce key cytokines (TNF-α, INF-α, INF-γ, IL-6, IL-1β) that activate myeloid dendritic cells. Activated dendritic cells present antigens (APCs) and secrete mediators such as IL-12 and IL-23, leading to the differentiation of Th1 and Th17 cell. Their inflammatory mediators (IL-17, IL-22) activate keratinocytes and induce the production of antimicrobial peptide, proinflammatory cytokines (TNF-α, IL-6), chemokines and S100 proteins. Thus, a rich interface between key cells and mediators of the innate and adaptive immune system is responsible for the psoriatic inflammatory process [3] (Fig. 1).

![Figure 1 – Immunopathogenesis of psoriasis, chronic cycle of inflammation](image)

Dendritic and T-cell activation is a critical component/event in disease pathogenesis. Dendritic cells are antigen-presenting cells (APCs), the major driver in bridging the gap between innate and adaptive immunity. Their increased number in psoriatic lesions induces autoproliferation of T-cells and Th-1 cytokines [3]. APCs are relevant in psoriasis because they are required for T-cell activation. In order to mediate the cellular changes in the dermis which lead to psoriasis, T-cells undergo 3 steps of interactions with other cell types. Firstly, APCs must be activated by one or more trigger factors in the epidermis, where antigen is internalized, enzymatically processed and presented on the APCs surface. APC displays antigen on its surface in the format of conjunction with MHC (Antigen/MHC) that the T-cell receptor (TCR) can recognize. After that, activated APCs travel/move to the lymph nodes where they induce activation, differentiation of naïve T-cells into one of many potential effector subtypes (Th17/Tc17 and type Th1/Tc1) and undergo clonal expansion [3, 15]. During this activation, T-cells and APC bind to each other at many points on their surfaces by means of receptor-ligand pairs. The first binding event is recognition of intracellular adhesion molecule-1 (ICAM-1) on the surface of the APC by lymphocyte function-associated antigen-1 (LFA-1) on the surface of the T-cell. An additional immunological synapse is binding of the leukocyte function antigen-3 (LFA-3) on the APC to the CD2 antigen on the T-cell. Dendritic cells (APCs) produce cytokines (IL-1, TNF-α, IL-6, IL-12, IL-23) that define the different T-helper cell types and drive T-cell differentiation [6]. Interleukin-12 (IL-12) stimulates differentiation into Th1 cells, whereas
IL-23 and IL-1β cause differentiation into Th-17 [3, 6]. Both T-cell subtypes (Th1, Th17) are found within psoriatic skin and each of them produces one or more specific cytokines. The final effect of all these immunologic synapses is activated effector T-cells with enhanced affinity for endothelial cells of skin capillaries. That process is mediated by binding between T-cell LFA-1 and endothelial ICAM-1.

Angiogenesis – the growth and remodelling of blood vessels with enhancement of vascular permeability – is mediated by adhesion molecules, including E-selectin, intercellular adhesion molecule-1(ICAM-1), vascular cell adhesion molecule-1 (VCAM-1) and VEGF (vascular endothelial growth factor) [6, 16].

The next step is trafficking of T-cells to the dermis and epidermis and T-cell reactivation, proliferation and cytokine production. This transport of T-cells into the epidermis is controlled by the interaction of αβ integrin (very late antigen 1 [VLA-1]) on T-cells with collagen IV in the basement membrane of the psoriatic epidermis [3]. Once in the skin, the activated T-cell undergoes a second activation (reactivation) similar to the previous encounter with APCs in the lymph node. Reactivated T-cells are then able to produce cytokines. Th1-cells predominantly secrete interferon-gamma (INF-γ), and tumour necrosis factor alpha (TNF-α), both have the central role of proinflammatory cytokines. Th-17 cell derived cytokines (IL-17A, TNF-α, IL-17F, IL-22), drive keratinocyte proliferation and inflammation in psoriatic plaque [18]. The immunological synapse in psoriasis results in the releasing of cytokines such as INF-γ, TNF-α, IL-12, IL-23, chemokines (CXCL8 – CXCL11 and CCL20) and S100 proteins [3].

Monocyte migration from the vascular pool to become tissue macrophages and neutrophil infiltration are stimulated by chemokine and IL-8. ICAM-1 and IL-6 may also be involved in keratinocytes proliferation [6, 17]. Furthermore, as in the pathogenesis of psoriasis, TNF-α plays an important role in the pathogenesis of PsA. TNF-α is known to mediate inflammatory processes and to upregulate other proinflammatory cytokines (e.g. IL-1, IL-6, IL-8) that increase the production of matrix metalloproteases (enzymes that catalyze bone and cartilage erosion) by synovial chondrocytes, fibroblasts, and osteoblasts [18].

**Treatment and severity of psoriasis disease**

Psoriasis presents a considerable therapeutic challenge. Current ways of treating psoriasis are based on pathophysiological mechanisms: inhibiting basal stem keratinocyte hyperproliferation, promoting keratinocytes differentiation, blocking dermal T-cell activation and blocking cytokines and other bioactive molecules that initiate the immunoinflammatory processes.

Each patient with psoriasis has his own, individual disease and treatment response. When developing a treatment schedule, it is necessary to: separate patients with mild localized psoriasis from patients with moderate to severe disease, consider triggering factors, comorbidities, comediations and the patient’s personality because of compliance.

Therapeutic responsiveness and contraindications in every individual patient are also important in the selection of therapy.

The Psoriasis Area Severity Index (PASI) is a clinical tool used to evaluate psoriasis severity and extensity [19]. Disease severity is estimated according to the PASI score as: 0–3 = very mild; 3–10 = mild; 10–18 = moderate; > 18 = severe. PASI is also standard in evaluating the efficacy of psoriasis treatment in clinical trials.

General recommendations for the treatment of mild-to-moderate psoriasis are topical antipsoriatics, for moderate- to-severe disease (with/without psoriatic arthritis) – conventional systemic drugs, photo(chemo)-therapy and biologic agents [1].

**Biological immunotherapy of psoriasis**

Advance in understanding of the immunopathogenetic process of psoriasis has suggested several new targets for therapeutic interventions and has contributed to the development of biological therapeutic agents. The biologics are so designed as to target specific components of the immune system – an immune or genetic mediator. They have a revolutionary technological advantage over the traditional immunosuppressive medications [20]. Biological agents are proteins derived from living sources such as humans, animals, plants and micro-organisms or synthesized through recombinant DNA techniques [5]. There are several distinct types of molecules developed for use in psoriasis: recombinant proteins, monoclonal antibodies, fusion proteins and toxin labelled proteins [5, 22]. The first biological agents that were approved for the treatment of psoriasis were T-cells-targeted therapies, disrupted activation and migration of T-cells (alefacept and efalizumab). After that, the agents – anticytokine therapies (anti-tumour necrosis factor), the group of etanercept, infliximab, and adalimumab have appeared and recently, ustekinumab, acting against p40 subunit of interleukin 12 and 23.

This article is focusing on the principles of biological therapy in psoriasis. Biological therapy has opened a new era in managing psoriasis. Fol-
lowing the principles and therapeutic guidelines enables the clinician to increase efficacy and safety in psoriasis, to prevent potential side-effects and complications, respecting the rule primum nil nocere.

**Biologics in psoriasis/psoriatic arthritis-general recommendations for clinician and patient**

The availability of biologics is a new, better treatment option for psoriatic patients, avoiding the cumulative toxicity associated with older systemic therapies. It is also a good alternative for those patients who are unresponsive or contraindicated to other treatment modalities.

In developing a treatment protocol with biologics, the main principles should be followed by the clinician and patient are:

1. Eligibility criteria: adults with moderate to severe chronic plaque psoriasis (PsA score ≥ 10), duration of at least 6 months, where the systemic therapy/phototherapy is either contraindicated, not tolerated or unresponsive, and patients who have not achieved the desired response with other psoriasis therapies [1, 21].

2. Exclusion criteria: pregnancy or breastfeeding, and patients with serious active infections.

3. Patient’s medical history, physical examination, and results from laboratory investigation at baseline.

4. The choice of the biological drug will depend on the clinical pattern of the psoriasis, pre-existing diseases/comorbidities and risk factors, patient’s/clinician’s preference and local facilities.

5. Before and during treatment, the monitoring investigations include full blood count, kidney and liver function tests, tuberculosis (TB) testing, and chest X-ray. Periodically a reevaluation for the development of new symptoms including infection and malignancy.

6. The biological therapies may impair the immunological response to vaccinations and therefore administration of live vaccines must be avoided during the treatment; vaccines should be applied before starting treatment with biologics.

**T-cell Inhibiting Agents**

T-cell targeted agents such as alefacept and efalizumab (which has been withdrawn from the market) have validated the immunopathogenesis concept of psoriasis and the critical role of T-cells in established disease. The mechanisms of action of these biologic agents include blockade of interactions leading to T-cell activation and reduction of pathogenic T-cells.

*Alefacept*

Alefacept is a fully humanized recombinant fusion protein that consists of LFA-3 and is linked to the Fc portion of IgG1. It selectively inhibits memory-effector T-cell activation/proliferation and produces apoptosis of this T-cell subset, by blocking LFA-3/CD2 interaction, via binding to CD2 on memory T-lymphocytes [23]. The selective effect of alefacept spares naïve T-cell while selectively reducing CD4+ and CD8+ memory T-cells [24, 25].

*Efalizumab*

Efalizumab was recently withdrawn from the market, because it carries the potential of causing progressive multifocal leukoencephalopathy (PML), a progressive neurological disease that is usually fatal. Efalizumab was specific to the CD11a subunit of LFA-1.

**Anti-TNF Agents**

TNF-α seems to play a crucial role in the pathogenesis of psoriasis and psoriatic arthritis. TNF is released from cells as a soluble cytokine (sTNF) following cleavage from its cell surface-bound precursor (transmembrane TNF, tmTNF). Both sTNF and tmTNF are biologically active, and bind to either of two distinct receptors: TNF receptor 1 (TNFR1, p55) and TNF receptor 2 (TNFR2, p75) [21]. To date, there are two groups of biological agents that target TNF: sTNF receptors (etanercept) and anti-TNF monoclonal antibodies (infliximab and adalimumab), approved for psoriasis/PsA treatment by the EMEA and FDA. All three agents neutralize the biological activity of TNF-α by binding with high affinity to the soluble and transmembraneous forms of TNF-α and inhibits binding of TNF-α with its receptors.

They are suggested for induction therapy for moderate to severe psoriasis when the response to phototherapy is poor. Therapy and conventional systemic agents has failed or they are contraindicated or not tolerated.

*Etanercept*

Etanercept is an immunoglobulin/receptor fusion protein of human TNF-α receptor (p75) linked with Fc portion of IgG1 that bind to soluble and membrane bound TNF-α [27, 30]. The approved treatment regimen of etanercept is 25 or 50 mg, both given twice weekly, self-administered subcutaneously (SC), for 12 weeks. If the etanercept-treated patient with a dose of 25 mg twice weekly, achieves PASI 75 reduction by week 12, the same dosage continues. If the patient achieves PASI 50 reduction by week 12, the recommended maintenance dose of etanercept is 50 mg twice weekly for up to 24 weeks [26]. Thus, the efficacy of etanercept is dose-dependent and has been demonstrated in many clinical trials. The randomized, double-blind, placebo-controlled trial with etanercept (biweekly subcutaneous injection
of 25 mg or 50 mg) reports that it is superior to a placebo in achieving PASI 75 reduction [27]. At week 12 of treatment, the PASI 75 was reported at 34% and 49%, respectively for above-mentioned doses, while the placebo group had PASI 75 of 4% [27–29]. At week 12, patients in the placebo group crossed over to etanercept therapy and all treatment groups were followed to 24 weeks. The efficacy continued to increase. At week 24, the percentage of patients with PASI 75 was 44% of those in the 25 mg twice weekly group, and 59% in the 50 mg/twice weekly dose treatment group. [27]. Etanercept was well tolerated during this study, with the most commonly reported adverse events being injection-site reactions, headaches and upper respiratory infections. Although the safety of etanercept has been established in clinical trials, certain recommendations should be considered. Baseline monitoring of PPD (purified protein derivation), liver function tests and complete blood cell count should be taken before prescribing this medication [1, 21]. Rare cases of tuberculosis have been reported in patients treated with TNF antagonists, including etanercept [30]. Ongoing monitoring such as periodic history and physical examinations are recommended while on treatment [1].

The efficacy and safety of etanercept has also been assessed in patients with psoriasis and PsA over a duration of 24 weeks [31]. Two different etanercept regimens were compared: 50 mg twice and 50 mg once weekly for 12 weeks, followed by 50 mg once weekly for the next 12 weeks. At 12 weeks of treatment, the response to etanercept regarding PsA response criteria (PsARC) was high and similar in the two groups (77% twice weekly group and 76% once weekly group). However, there was significant improvement of psoriasis according to the PGA (physician global assessment) in the twice weekly group – 46% than in the once weekly group – 32%. According to the results, a 50 mg twice weekly etanercept dose relieves psoriasis symptoms more quickly than 50 mg once weekly, but the latter, 50 mg once weekly, was sufficient for treating PsA symptoms.

Etanercept should be considered the first choice drug for patients with significant, uncontrolled psoriatic arthritis. Some patients showed a decrease of clinical response after 12 weeks when the weekly dose was reduced from 50 mg twice to 50 mg once weekly. If the induction therapy is estimated as successful after 10 to 16 weeks of treatment, maintenance therapy with the lowest effective dose should be considered [26].

Rebound does not occur after discontinuation of treatment, although there may be a lower response rate on restarting therapy [21, 32].

Antibody formation against etanercept ranged from 1.1 to 18.3 [32, 33].

A small number of studies reported [34, 35] that a combination of etanercept with methotrexate in psoriasis significantly increased efficacy at 24 weeks, and a loss of efficacy when methotrexate was discontinued. Methotrexate could be recommended as comedication with etanercept in PsA, in order to improve efficacy in certain clinical circumstances of psoriasis [21].

The early data from Gisondi’s study suggested that a combination of etanercept 25 mg once weekly with acitretin 0.4 mg/kg daily is as effective as etanercept 25 mg twice weekly, and that both medications are more effective than acitretin alone. This combination may offer additional efficacy, and without possibility of additional toxicity [36].

**Infliximab**

Infliximab is a chimeric (human-murine) monoclonal antibody against TNF-α. It is given in a dose of 5 mg/kg as an intravenous infusion (IV) over 2–3 hours, at weeks 0, 2, and 6 and then every 8 weeks for psoriasis and psoriatic arthritis [37]. Infliximab is useful in clinical circumstances requiring rapid disease control, e.g. in unstable erythrodermic or pustular psoriasis, due to its very rapid action onset and high response rate (within 1–2 weeks) [26].

The efficacy of infliximab in patients with severe psoriasis was the focus of analysis of SPIRIT (Study of Psoriasis with Infliximab Remicade Induction Therapy) and EXPRES (European Infliximab for Psoriasis (Remicade) Efficacy and Safety Study) studies [38, 39]. The majority of patients had previously received phototherapy or systemic therapy, without satisfactory results. Data from the SPIRIT study [38] showed that Infliximab given as a monotherapy in a dose of 3 mg, and 5 mg vs placebo, resulted in a significant increase in the number of patients who achieved PASI 75 reduction, in the first group 72%, the second group 88%, and in the placebo group 6% at week 10. At week 10 evaluation, a significant clinical benefit and rapid response time was seen in the infliximab groups compared to the placebo. Efficiencies were maintained over the placebo for 46–50 weeks, loss of efficiencies over time may also occur with infliximab therapy. 80% of patients on infliximab reached PASI 75 within 10 weeks, but this response decreased over time. After 50 weeks, the number of patients who lost infliximab response was reduced to 61% [39]. In the responders, subsequent infusions should be given at 8-week intervals to maintain disease control although long-
term data are available only up to 1 year [21]. If induction therapy is successful after 10 to 16 weeks of treatment, a maintenance therapy could be considered [26].

A loss of response was noted in those subjects who developed anti-infliximab antibodies, which occurred in 19% of patients treated, associated with a higher rate of infusion reactions [39, 41]. The investigated comparison between continuously (every 8 weeks) and intermittently (as required) infliximab therapy showed that a continued standard course produced a better level of response [40].

Low-dose methotrexate could be recommended as comedication to improve efficacy or to reduce the development of infliximab-antibodies [21].

Many clinical studies confirm the efficacy of infliximab in chronic plaque type psoriasis, but only a small number of reports describe the effects of infliximab in severe pustular and erythrodermic psoriasis. Pustular and erythrodermic psoriasis can be a debilitating and recalcitrant disease which may result in secondary complications such as sepsis, electrolyte imbalance, renal failure, and heart failure.

Infliximab is a therapeutic option for severe therapy-resistant pustular psoriasis because a single well-tolerated dose significantly ameliorates the patient’s condition. Treated patients showed significant improvement of skin eruption and general condition within three days after treatment without any side-effects [42]. There is a report of a 46-year-old patient with life-threatening erythrodermic psoriasis who responded rapidly to intravenous infliximab [43].

Concomitant systemic therapies may be indicated for some patients with very severe or unstable psoriasis, although doses of these should be minimized [21].

Key safety considerations for infliximab include common side-effects, mainly infections and infusion reactions, as well as rare opportunistic infections, particularly tuberculosis. The relationship between infliximab and some other significant adverse events observed infrequently during the treatment, including cases of severe liver toxicity, demyelinating diseases, or lymphoma, is less clear. Nevertheless increased caution is always advisable.

**Adalimumab**

Adalimumab is a fully human monoclonal antibody IgG1 against TNF-α. Adalimumab is recommended for induction therapy of moderate to severe psoriasis and psoriatic arthritis if photo(chemo)therapy and conventional systemic agents have had an inadequate response or if they are contraindicated/not tolerated. The dosage is 80 mg subcutaneously (SC) in the first week followed by 40 mg the following week and then 40 mg every 2 weeks thereafter. In the case that, after 10 to 16 weeks, induction therapy is estimated as successful, maintenance therapy can be considered, but with the lowest effective dose [26]. In phase II study, different dose regimens of adalimumab were compared, 40 mg weekly and 40 mg every other week vs placebo. After 12 weeks of therapy a dose response was estimated: in the placebo group PASI 75 was observed in 4%, in the weekly dose group 80% of patients achieved PASI 75% and in the last group with alternate week dose regimen 53% of patients showed PASI 75 [44]. In the phase III studies, 1,212 patients were randomized in order to evaluate the efficacy and safety of adalimumab treatment of moderate to severe psoriasis and to compare continuous vs interrupted therapy [45]. At week 16, 71% of patients treated with adalimumab and 7% of placebo-treated patients achieved 75% improvement in the PASI score (PASI 75%). During weeks 33 to 52, the percentage of patients receiving adalimumab who lost adequate response, was 28% compared to 5% treated continuously with adalimumab [45]. So, the recommendation is for adalimumab to be used continuously in a dose of 40 mg every other week after an initial dose. Short-term results: 80% of patients achieved PASI-75 at week 12, long-term results were noted in 68% of patients who achieved PASI-75 at week 60. A small percentage of patients treated with adalimumab lost efficacy with continued use [1].

Anti-adalimumab antibodies developed in 8.4% of patients, resulting in increased clearance and reduced efficacy of adalimumab [21]. If necessary, treatment may be discontinued without risk of disease rebound, although there may be a lower response rate on restarting therapy [21].

Saurat et al. compared the efficacy of adalimumab vs methotrexate in chronic plaque psoriasis [46]. At 16 weeks, 80% of patients on adalimumab achieved PASI 75 vs 35.5% of patients treated with methotrexate. This study suggests that adalimumab is superior in efficacy compared with methotrexate in psoriasis treatment. Methotrexate may be a recommended comedication in certain clinical circumstances, e.g. in associated arthropathy, or in order to increase treatment efficacy [21].

In placebo-controlled phase III study, Choy et al. [47] presented 24 and 48-week data on the efficacy of adalimumab in psoriatic arthritis. Regardless of disease duration, PASI 50, 75, 90 scores were significantly better in patients treated with adalimumab as compared to those on placebo, at 24 weeks. This response was sustained at 48 weeks. Additionally, patients receiving adalimumab exhibited better ACR (American College of Rheumatology) 20, 50 and 70 response rates at week 24 as compared to patients receiving pla-
Well tolerated and efficacious in treating PsA. PASI 75 at 24 weeks vs. 1% of the 69 patients treated with placebo. Of the 69 patients treated with adalimumab and evaluated for PASI, 59% achieved significantly higher in the adalimumab than in the placebo group. Of the 69 patients treated with placebo, 3% achieved PASI 75 at 24 weeks vs. 1% of the 69 patients treated with placebo (p < 0.001). Adalimumab was well tolerated and efficacious in treating PsA during the 2-year period [48].

In placebo-controlled trials, injection-site reactions were the most frequently reported adverse drug reactions, occurring in 20% of patients treated with adalimumab compared to 14% receiving placebo. Adalimumab could show infectious adverse effects such as upper respiratory tract and urinary infections. More serious infections were also observed as a pneumonia, septic arthritis, erysipelas, cellulitis, diverticulitis, and pyelonephritis. Severe allergic reactions to adalimumab are rare.

Adalimumab therapy may result in the formation of autoantibodies and (rarely) development of a lupus-like syndrome.

The role of adalimumab in the development of malignancies is unknown; lymphoma was registered very rarely [26].

Anti-p40 (IL-12/IL-23)

Biologics targeting the p40 chain to both IL-12 and IL-23 have either been approved for the treatment of moderate to severe plaque psoriasis in adults (ustekinumab) or are in Phase III clinical trials (ABT-874 [briakinumab]). This therapeutic approach is conceptually new, since it targets mainly dendritic-cell-derived cytokines IL-12 and IL-23.

Ustekinumab

Ustekinumab is the first of a new class of biological drugs that prevent actions of cytokines IL-12 and 23, responsible for T-cell activation and differentiation into one of many potential effector subtypes Th1, Th2, Th17 [6].

Ustekinumab is administrated subcutaneously in a dose of 45 mg at week 0, followed by a 45 mg dose at week 4, and every 12 weeks thereafter. For patients with body weight > 100 kg, 90 mg resulted in greater efficacy; however, 45 mg was also shown to be effective [49]. Consideration should be given to discontinuing treatment in patients with no response up to 28 weeks of treatment.

The approval of ustekinumab is based on data from two large, pivotal Phase III, multi-centre, randomized, double-blind, placebo controlled trials (PHOENIX 1 and 2) involving nearly 2000 patients. The efficacy and safety of ustekinumab in the treatment of moderate to severe plaque psoriasis were evaluated [50, 51, 52]. In the PHOENIX 1 study the patients were randomized in 3 groups: one on a dose of 45 mg, the second on 90 mg subcutaneously injected ustekinumab at weeks 0, 4, then every 12 weeks and the last group on placebo. At week 12, PASI 75 achieved 67% of patients in the ustekinumab 45 mg; 66% in the group with ustekinumab 90 mg and 3.1% receiving placebo [51].

Similar results were observed in the PHOENIX 2 study, designed as PHOENIX 1, but with a larger number of patients. In this study, the increasing dose of ustekinumab in partial responders (achieving PASI 50–75) was investigated. The full responders are subjects that achieved PASI 75 by week 28 and partial responders are defined as subjects who achieved PASI 50 at week 28. At week 12, 66% and 76% of patients receiving ustekinumab 45 mg or 90 mg doses, respectively, achieved PASI 75 compared with 4% of patients on placebo. At week 28 partial responders were re-randomized to continue dosing every 12 weeks or to escalate dosing to every 8 weeks. The investigators noted that dose escalation proved more effective than continuing the same dose in partial responders. At week 52, 69% of partial responders in the ustekinumab 90 mg group every 8 weeks achieved PASI 75, versus 35% receiving the same dose every 12 weeks. However, there was no difference in partial responders who received ustekinumab 45 mg. Partial responders had increased the prevalence of antibodies against ustekinumab. The majority of responders receiving injections every 12 weeks maintained PASI 75 response up to 18 months.

Rates of adverse events, including serious infections such as tuberculosis, malignancies and cardiovascular symptoms, were low and consistent with the expected background rates. The most common adverse reactions in Phase III clinical trials were arthralgia, cough, headache, injection site erythema, nasopharyngitis and upper respiratory tract infection. Most side-effects were considered to be mild and did not necessitate discontinuation of the therapy.

The results of these two clinical studies indicate that ustekinumab was effective in treating moderate to severe psoriasis, but changing the recommendation dose treatment from every 12 weeks to every 8 weeks may be required in partial responders.

Some patients with psoriatic arthritis do not respond to usual drug treatments, so alternatives are needed. Findings suggest that interleukins 12 and 23 might affect clinical symptoms and pathological joint changes in psoriatic arthritis. The efficacy and safety of ustekinumab for psoriatic arthri-
tis was assessed in this phase II study [53]. Patients with active psoriatic arthritis were randomized to either ustekinumab (90 mg or 63 mg) every week for 4 weeks (weeks 0–3) followed by placebo at weeks 12 and 16 (n = 76; Group 1) or placebo (weeks 0–3) and ustekinumab (63 mg) at weeks 12 and 16 (n = 70; Group 2). The primary endpoint was ACR 20 response at week 12. An ACR 20 response was recorded in 42% of patients with ustekinumab and 14% in the placebo group at week 12.

During the placebo-controlled period (weeks 0–12), adverse events arose in 46 (61%) patients in Group 1 and 44 (63%) in Group 2; serious adverse events were recorded in three (4%) Group 2 patients. Ustekinumab significantly reduced signs and symptoms of psoriatic arthritis, but larger and long-term studies are needed for further confirmation of ustekinumab efficacy and safety [53].

**ABT-874**

ABT-874 is another antibody generated to block the action of IL-12 and IL-23 by binding to their subunit p40.

Table 1

<table>
<thead>
<tr>
<th>Description Mechanism</th>
<th>Alfacet</th>
<th>Etanercept</th>
<th>Infliximab</th>
<th>Adalimumab</th>
<th>Ustekinumab</th>
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<tbody>
<tr>
<td>Dosing</td>
<td>25 mg SC 2 x/wk</td>
<td>5 mg/kg at weeks 0, 2, 6; then every 8 weeks IV over 2–3h</td>
<td>80 mg SC at week 0 then 40 mg e.o.w. from week 1</td>
<td>45 mg SC at week 0, 4; then every 12 weeks 90 mg SC at week 0, 4; then every 12 weeks</td>
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<td>PP and/or CXR, routine CBC</td>
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<td>Side effects</td>
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<td>Injection site reactions, positive ANA, infections/sepsis, malignancy</td>
<td>Injection site reactions, positive ANA, infections/sepsis, malignancy</td>
<td>Serious infections/tuberculosis, malignancy, cardiovascular symptoms</td>
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<td>Hypersensitivity to infliximab, active infections or sepsis, congestive heart failure, live vaccines</td>
<td>Hypersensitivity to adalimumab, active infections or sepsis, live vaccines</td>
<td>Hypersensitivity to ustekinumab, active infections or sepsis, live vaccines</td>
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**In Phase II, a 12-week, multicentre, randomized, double-blind, placebo-controlled trial, the efficacy and safety of ABT-874 in psoriasis was investigated [54].**

One hundred and eighty patients with clinically stable moderate to severe chronic plaque psoriasis were randomized in groups of 30 to receive 1 of 6 treatments with ABT-874 provided as a SC injection: one 200 mg dose at week 0; 100 mg every other week for 12 weeks; 200 mg weekly for 4 weeks; 200 mg every other week for 12 weeks; 200 mg weekly for 12 weeks; or placebo. The percentage of patients achieving a 75% reduction in the PASI at week 12 was statistically significantly greater in all the ABT-874 treatment groups than in the placebo group. The authors of the study concluded that ABT-874, an interleukin 12/23 monoclonal antibody, was highly effective and well tolerated in the treatment of psoriasis, but long-term studies are required to confirm these findings [54].

The main features of biologics in psoriasis are shown in Table 1.

### The main features of biologics in psoriasis

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<th>Alfacet</th>
<th>Etanercept</th>
<th>Infliximab</th>
<th>Adalimumab</th>
<th>Ustekinumab</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Indications</strong></td>
<td>FDA: Plaque psoriasis</td>
<td>Plaque psoriasis, psoriatic arthritis</td>
<td>Plaque psoriasis, erythrodermic or pustular psoriasis and psoriatic arthritis</td>
<td>Plaque psoriasis, and psoriatic arthritis</td>
<td>Plaque psoriasis and psoriatic arthritis</td>
</tr>
<tr>
<td><strong>Dosing</strong></td>
<td>IM/IV 7.5 mg qwk x 12 wk (in office)</td>
<td>25 mg SC 2 x/wk or 50 mg SC 2 x/wk x 12 weeks</td>
<td>5 mg/kg at weeks 0, 2, 6; then every 8 weeks IV over 2–3h</td>
<td>80 mg SC at week 0 then 40 mg e.o.w. from week 1</td>
<td>45 mg SC at week 0, 4; then every 12 weeks 90 mg SC at week 0, 4; then every 12 weeks</td>
</tr>
<tr>
<td><strong>Monitoring</strong></td>
<td>PPD and/or CXR, BUN, SGOT, SGPT, CBC</td>
<td>PP and/or CXR, BUN, SGOT, SGPT, CBC</td>
<td>PP and/or CXR, routine CBC</td>
<td>PPD and/or CXR, routine CBC</td>
<td></td>
</tr>
<tr>
<td><strong>Side effects</strong></td>
<td>Injection site reactions, cough and respiratory symptoms, infections, headaches, positive ANA</td>
<td>Injection site reactions, positive ANA, infections/sepsis, malignancy</td>
<td>Injection site reactions, positive ANA, infections/sepsis, malignancy</td>
<td>Serious infections/tuberculosis, malignancy, cardiovascular symptoms</td>
<td></td>
</tr>
<tr>
<td><strong>Contraindications</strong></td>
<td>Hypersensitivity to etanercept, active infections or sepsis, congestive heart failure, live vaccines</td>
<td>Hypersensitivity to infliximab, active infections or sepsis, congestive heart failure, live vaccines</td>
<td>Hypersensitivity to adalimumab, active infections or sepsis, live vaccines</td>
<td>Hypersensitivity to ustekinumab, active infections or sepsis, live vaccines</td>
<td></td>
</tr>
</tbody>
</table>

### Conclusions

Understanding psoriatic disease on the molecular level has resulted in the development of a new class of therapies, the biologics, designed specifically against/towards the immunopathologic hallmarks of psoriatic process. Biologics namely target different cellular and molecular effector mechanisms. They have opened a new era in psoriasis management, a new opportunity and hope for patients suffering from severe and recalcitrant psoriasis forms.
Different efficacy/safety profiles between biologic agents gives the clinician the choice to individualize the therapy for each psoriatic patient.

Although biologics are well-established tools in the therapeutic armamentarium for psoriasis, clinicians are still gathering experience, searching for the best treatment schedules/protocols for patients with psoriasis/psoriatic arthritis.

REFERENCES


32. Tyring S, Gordon KB, Poulin Y, Langley RG, Gottlieb AB, Dunn M, et al. Long-term safety and efficacy of 50mg of etanercept twice weekly in pa-

47. Choy E, Gladman D, Sasso E. Efficacy of adalimumab by disease duration in psoriatic arthritis: Subanalysis of ADEPT. Presented at: 65th Annual Meeting of the AAD; Feb 1–6, 2007; Washington, DC; Poster 2748.


The document discusses principles of biological therapy in psoriasis. It highlights the role of cytokine signals between effector Th1 and Th17 cells, dendritic cells, and regulatory T-cells as well as macrophages in the release of cytokines responsible for hyperproliferation and abnormal differentiation of epidermal keratinocytes.

Modern insights into the immunopathogenesis and inflammatory cytokines have provided a foundation for the development and introduction of biological drugs in the treatment of moderate to severe psoriasis and psoriatic arthritis.

These drugs, such as alefacept, etanercept, adalimumab, infliximab, and ustekinumab, target different points in the immune system, offering efficacy, safety, and recommended dosages to patients.

The goal of the presented therapeutic recommendations is to ensure a high standard of continued effective and safe therapy for patients with cutaneous psoriasis and psoriatic arthritis.

**Keywords:** psoriasis, immunopathogenesis, alefacept, etanercept, adalimumab, infliximab, ustekinumab.