# Biologic Agents for Psoriasis

# 137

Marina Papoutsaki and Christina Antoniou

**Key Points**

- The choice of treatment for psoriasis depends on the severity of the disease.
- The severity of psoriasis is not always easy to define as it depends both from the extension of the disease as well as its impact on the quality of life of the patients.
- The main target of almost all systemic treatments for psoriasis is the immune system.
- The introduction of biologics has brought an important therapeutic improvement for psoriasis.
- Biologics are a heterogeneous group of monoclonal antibodies, fusion proteins, and recombinant cytokines that modify and regulate pivotal and specific mechanisms involved in psoriasis' immunopathogenesis.
- At present, there are four biologics available for the treatment of psoriasis: three antitumor necrosis factor alpha (TNFα) agents, namely, adalimumab, etanercept, infliximab, and one anti-IL12/23 monoclonal antibody (mAb), ustekinumab.
- Patient candidates for a biological treatment need to undergo a detailed screening and a regular follow-up, in order to guaranty a good safety profile.
- Biologics show high efficacy both in the short and in the long term and a good safety profile.
- The better understanding of the pathogenetic mechanisms of psoriasis leads to continuous development of new therapeutic agents with very promising results.

## General Principles

The choice of treatment for psoriasis depends on the severity of the disease; nevertheless, the evaluation of its severity may result difficult in some cases as not only objective parameters (extension, erythema, infiltration, etc.), but also the impact on the quality of life of the patients must be taken into consideration. Indeed smaller lesions may cause a higher psychological or physical discomfort for the patient depending on their localization.

M. Papoutsaki (✉)
Department of Dermatology,
Dermatologist and Venereologist University,
Hospital "Andreas Syggros", Athens, Greece
e-mail: marinapapoutsaki@hotmail.com

C. Antoniou
Department of Dermatology,
University of Athens, Hospital "Andreas Syggros",
Athens, Greece
e-mail: christinantoniougr@yahoo.com

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Given the well-established role of the immunomediated inflammation in the pathogenesis of psoriasis, the immune system is the main target of almost all systemic treatments available for this disease.

Systemic agents, including cyclosporine, methotrexate, and acitretin, or phototherapy, are usually prescribed in patients affected by moderate to severe plaque-type psoriasis or psoriatic arthritis. However, various factors may limit their long-term use, in particular the risk of serious cumulative organ toxicity and the lack of efficacy over time. Furthermore, underlying diseases, such as hypertension as well as renal and/or hepatic alterations, may represent contraindications to the abovementioned systemic treatments. Thus, effective drugs with less long-term toxicity are needed.

An excellent therapeutic improvement has been recently obtained by the introduction of the "biological response modifiers" or more commonly defined as "biologics." Biologics are a heterogeneous group of monoclonal antibodies, fusion proteins, and recombinant cytokines, designed to modify and regulate pivotal and specific mechanisms involved in psoriasis immunopathogenesis. To date, biologics have been suggested to have a more favorable side effect profile than conventional treatments.

## Biological Agents for the Treatment of Psoriasis

Numerous biologics are approved by FDA or EMA and are actually being used for the treatment of psoriasis. These biologics include three antitumor necrosis factor alpha (TNFα) agents, namely, adalimumab, etanercept, infliximab, and one anti-IL12/23 monoclonal antibody (mAb), ustekinumab. All three anti-TNFα agents and the anti-IL12/23 agent, ustekinumab, are now commercially available for the treatment of both psoriasis and/or psoriatic arthritis.

## Anti-TNF-a Agents

### Etanercept

#### Mechanism of Action

Etanercept is a dimer of a chimeric protein genetically engineered by fusing the extracellular ligand-binding domain of the human TNF receptor 2 and the Fc domain of human IgG1 antibody (including the hinge and CH2 and CH3 regions but not the CH1 region). Because of its structure, etanercept binds and neutralizes the inflammatory cytokines TNF-α and lymphotoxin-alpha (TNF-beta). As a soluble receptor, etanercept binds free but not transmembrane TNF-α and therefore blocks the inflammatory cascade triggered by TNF-α leading to anti-inflammatory and immunosuppressant activity.

Its terminal elimination half-life is about 4–5 days.

#### Indications

Etanercept has been approved for moderate to severe plaque-type psoriasis and psoriatic arthritis, in whom other systemic therapies and phototherapy have failed, are contraindicated, or not tolerated. Moreover, etanercept is the only anti-TNFα agent approved for the treatment of childhood psoriasis (in children over 6 years of age) and psoriatic arthritis (in children over 12 years of age) nonresponsive or intolerant to traditional systemic therapies or phototherapy.

#### Dosage and Mode of Administration

Etanercept is self-administrated subcutaneously.

*Initial dose*: 25 mg twice weekly or 50 mg once weekly or 50 mg twice weekly for the initial 12 weeks and then reduce to 25 mg twice weekly or 50 mg once weekly. However, the 50 mg/twice weekly seems to have stronger clinical activity. Pharmacokinetic modeling and simulation, as well as clinical studies, suggest that the systemic exposure is equivalent for the 25 mg twice weekly and the 50 mg once weekly regimens. Its efficacy and safety for the different dosing have been demonstrated in several randomized clinical trials.

For childhood psoriasis, the suggested dosage regimen is 0.8 mg/kg (up to a maximum of 50 mg of a single dose) once weekly.

*Maintenance dose:* 25 mg twice weekly or 50 mg once weekly after 12 weeks of treatment.

#### Combination Therapy

Etanercept is usually used in monotherapy. Nevertheless, the concomitant use of topical antipsoriatic therapies (topical steroids, vitamin

$D_3$ derivatives, tazarotene, dithranol) may be feasible and advisable especially in the early stages of treatment or in the cases of mild recurrences of the disease during the maintenance period.

Regarding its combination with other systemic antipsoriatic agents, MTX is an established association in the treatment of psoriatic arthritis, and it can be used also in plaque-type psoriasis. Successful association also with acitretin has been reported in the literature, while there are as yet no validated data on combination therapy with fumaric acid esters or cyclosporine.

### Side Effects

The most commonly reported side effects reported are local reactions in the injection site. In patients receiving anti-TNFα agents, as etanercept, there is a higher risk of developing infections. The most common infections observed are these of the upper respiratory tract, bronchitis, and skin infections. Severe infections including sepsis, tuberculosis, demyelinating processes, vasculitis, pancytopenia, anemia, leukopenia, lupus erythematosus, thrombocytopenia, and urticaria are rare.

### Drug Interactions

The use of etanercept is not advised in patients who are treated with anakinra (IL-1 R antagonist) or abatacept as an increased number of serious infections and neutropenia have been reported.

## Infliximab

### Mechanism of Action

Infliximab is a chimeric (25 % mouse, 75 % human) monoclonal IgG1 antibody able to bind TNF-alpha (transmembrane and soluble form) and, consequently, to inhibit TNF-alpha activity. In particular its binding blocks soluble TNF-α, neutralizing this way its proinflammatory activity, while binding to membrane cell-bound TNF-α leads to cell elimination, possibly as a result of complement activation and/or antibody-dependent cellular toxicity or induction of apoptosis.

Infliximab was the first anti-TNF-alpha therapy successfully used in psoriasis, in a woman affected also by refractory inflammatory bowel disease, and therefore treated with infliximab 5 mg/kg. Several studies show that infliximab acts on multiple steps of the pathogenic process of psoriasis.

### Indications

Infliximab is approved for the treatment of psoriatic arthritis and plaque-type psoriasis.

### Dosage and Mode of Administration

Infliximab is administered intravenously, and the dosage used for the treatment of plaque-type psoriasis is weight dependent.

*Initial dose*: There is an induction period with the dose regimen of 5 mg/kg at weeks 0, 2, and 6, followed by a maintenance dose.

*Maintenance dose:* The dose regimen is of 5 mg/kg every 8 weeks. This interval may be temporarily shorten up to every 6 weeks in these patients that present a time-related recurrence of the disease, in order to regain the efficacy.

The efficacy and safety of infliximab has been evaluated in several clinical trials. Infliximab shows a fast efficacy in the treatment of plaque and psoriatic arthritis.

### Combination Therapy

Infliximab is usually used in monotherapy in plaque-type psoriasis. Nevertheless the concomitant use of topical antipsoriatic therapies (topical steroids, vitamin $D_3$ derivatives, tazarotene, dithranol) may be feasible and advisable especially in the early stages of treatment or in the cases of mild recurrences of the disease during the maintenance period.

Regarding its combination with other systemic antipsoriatic agents, MTX is an established association in the treatment of psoriatic arthritis, and it can be used also in plaque-type psoriasis. There are reports in the literature regarding its association also with acitretin (in particular in the case of recurrence of pustular forms of psoriasis) and cyclosporine.

### Side Effects

Acute infusion reactions are a commonly reported side effect of infliximab, but usually these reactions are mild and transitory and

include chills, headache, flush, nausea, dyspnea, or infiltration at the infusion site. Due to this, it is advisable to monitor carefully the patient during the infusion and for 1 h afterward. Serum sickness may occur 3–12 days following the infusion. The probability of an infusion reaction is higher in patients that have developed infliximab-specific antibodies and in patients receiving the drug after a long treatment-free interval. The administration of an antihistamine can help reduce or prevent a moderate infusion reaction. Other common reactions are exanthema, pruritus urticaria, and increased liver transaminase. In patients receiving anti-TNFα agents, as infliximab, there is a higher risk of developing infections. The most common infections observed are these of the upper respiratory tract, bronchitis, and opportunistic infections. Severe infections including sepsis, tuberculosis, demyelinating processes, vasculitis, pancytopenia, anemia, leukopenia, lupus-like syndrome serum sickness, onset or exacerbation of psoriasis (often pustular forms of the disease), thrombocytopenia, anaphylactic shock, and liver cell damage are rare.

### Drug Interactions

Based on the present information, no drug interactions of infliximab with other medications have been described. Nevertheless based on the reports that combination of etanercept with anakinra leads to a higher rate of serious infections, the combination of infliximab and anakinra is not advised.

## Adalimumab

### Mechanism of Action

Adalimumab is a fully human monoclonal antibody, genetically engineered using phage display technology, and it is structurally and functionally analogous to naturally occurring human immunoglobulins G1 (IgG1). This monoclonal antibody demonstrates a high specificity and affinity for TNFα but not other cytokines, such as lymphotoxin (LTβ).

### Indications

Adalimumab is approved for the treatment of psoriatic arthritis and plaque-type psoriasis.

### Dosage and Mode of Administration

Adalimumab is self-administrated subcutaneously.

*Initial dose*: The recommended dosing of adalimumab for the treatment of plaque-type psoriasis and psoriatic arthritis is an initial dose of 80 mg, followed by 40 mg the week after.

*Maintenance dose:* The maintenance dose is 40 mg/every other week starting from week 2. In some high-need patients, a dose regimen of 40 mg/weekly may be considered in order to enhance its efficacy.

The efficacy and safety of adalimumab has been evaluated in several clinical trials. Moreover, adalimumab was the first biological drug for which a comparative study with a conventional drug (methotrexate) has been performed.

### Combination Therapy

No controlled studies on combination therapy have been performed, and adalimumab is usually used in monotherapy in plaque-type psoriasis. Nevertheless the concomitant use of topical antipsoriatic therapies (topical steroids, vitamin $D_3$ derivatives, tazarotene, dithranol) may be feasible and advisable especially in the early stages of treatment or in the cases of mild recurrences of the disease during the maintenance period.

Regarding its combination with other systemic antipsoriatic agents, MTX is an established association in the treatment of psoriatic arthritis, and it can be used also in plaque-type psoriasis. There are anecdotal reports in the literature regarding its association also with acitretin (in particular in the case of recurrence of pustular forms of psoriasis) and cyclosporine.

### Side Effects

The most common adverse event reported from placebo-controlled clinical trials was injection site reactions, such as erythema, itching, pain, and swelling. Adalimumab can be associated with infectious adverse events, mainly of the upper respiratory tract, bronchitis, and urinary tract infections. Severe infections such as pneumonia, septic arthritis, postoperative infections, erysipelas, phlegmonous infections, diverticulitis, and pyelonephritis have also been described.

Thrombocytopenia and leukopenia have been rarely reported. Treatment with adalimumab may result in the formation of autoantibodies and infrequently in the development of lupus-like syndrome. Severe allergic reactions are rare and include exanthem, urticaria, pruritus, respiratory distress, tightness in the chest, as well as swelling of the mouth, face, lips, or tongue. Malignancy, especially lymphoma, is a very rare side effect.

#### Drug Interactions

The combination therapy with anakinra and abatacept may lead to serious infections, without any additional clinical benefit; therefore, their combination is not recommended.

## Anti-IL12-23 Agents

### Ustekinumab

#### Mechanism of Action

Ustekinumab is a human monoclonal antibody that binds to the shared p40 protein subunit of human interleukins 12 and 23 with high affinity and specificity, thereby preventing interaction with their surface IL.12Rβ1 receptor. In a population pharmacokinetic analysis based on data obtained from two pivotal large-scale phase III studies (PHOENIX 1, PHOENIX 2), different factors such as body weight, diabetes, and positive immune response (antibodies to ustekinumab) seem to be important covariates affecting the apparent clearance and/or apparent volume of distribution of ustekinumab.

#### Indications

Ustekinumab is approved for the treatment of psoriatic arthritis and plaque-type psoriasis.

#### Dosage and Mode of Administration

Ustekinumab is self-administrated subcutaneously at a dose of 45 or 90 mg according to the patient's weight (<100 kg or ≥100 kg).

*Initial dose*: The recommended dosing of ustekinumab for the treatment of plaque-type psoriasis and psoriatic arthritis is an initial dose of 45 or 90 mg, according to the patient's weight, at week 0 and 4.

*Maintenance dose:* The maintenance dose is 45 or 90 mg, according to the patient's weight, every 12 weeks.

The efficacy and safety of ustekinumab has been evaluated in several clinical trials.

#### Combination Therapy

There are no controlled studies on combination therapy; nevertheless, combination with topical antipsoriatic agents may be beneficial for the patient.

#### Side Effects

Infections are the most important side effect occurring with this drug. The most common infections observed were nasopharyngitis and upper respiratory tract infections, while the rate of severe infections was low. The data from the main clinical studies of ustekinumab (PHOENIX-1 and PHOENIX-2) show no association with lymphocytopenia nor any toxic cumulative effects. Moreover, the rate of reported malignancies was low and comparable either with the ones of the placebo population or the general population. The same applies also to the serious cardiovascular events observed, mainly during the first phase of the studies.

#### Drug Interactions

No chemical or via the cytochrome P450 system interactions are expected for ustekinumab.

## Patient Candidates for Biological Treatments

Candidates for biological treatments are patients affected by moderate to severe psoriasis (PASI >10 or BSA >10 and DLQI >10) for at least 6 months that fulfill one of the following criteria:

- Nonresponsive or intolerant to traditional systemic treatments (cyclosporine, methotrexate, acitretin, fumaric acid)
- Nonresponsive or intolerant to phototherapy (PUVA, UVB)
- Affected by instable or life-threatening forms of psoriasis

- Patients with severe impact on their quality of life
- Patients affected by psoriatic arthritis independently of the severity of their skin lesions

Nevertheless and according to the new concept of treatment goals in psoriasis, there are special clinical manifestations that may change the definition of a mild psoriasis into moderate to severe psoriasis leading to a significant impairment of their quality of life. These manifestations can include the following:

- Involvement of visible areas
- Involvement of major parts of the scalp
- Involvement of the genitals
- Involvement of the palm and/or soles
- Onycholysis or onychodystrophy of at least two fingernails
- Pruritus leading to scratching
- Presence of single recalcitrant plaques

## Patient's Screening and Follow-Up

Biological treatments have demonstrated a rather good safety profile in the long-term treatment compared with the traditional therapies. These drugs seem to lack specific organ toxicity unlike conventional treatments. Nevertheless due to their mode of action, adverse events may arise. In order to minimize their side effects, a careful screening of the patient prior to treatment is required.

## Patient's Screening

### Medical History and Physical Examination

Prior to treatment with a biological agent, a detailed medical history needs to be taken, and the following conditions need to be investigated:

- Presence of chronic or acute infections (tuberculosis, hepatitis B, hepatitis C, HIV)
- Presence or history of malignancies or lymphomas
- Presence of other autoimmune diseases
- Signs or positive family history of demyelinating diseases (especially in candidates of anti-TNFα agents)
- Presence or history of cardiovascular events
- Presence of comorbidities such as arthritis, diabetes, hypertension, obesity, hyperlipidemia, and depression

A list of the absolute and relative contraindications is given in Tables 137.1 and 137.2.

Physical examination is important in order to evaluate the severity of the disease as well as the presence of psoriatic arthritis. In order to evaluate the severity of the disease before treatment as well as to evaluate its efficacy during treatment, the following scores need to be assessed:

- BSA (Body Surface Area)
- PASI (Psoriasis Area Severity Index)
- NAPSI (Nail Area Psoriasis Severity Index)
- DLQI (Dermatology Life Quality Index)

**Table 137.1** Absolute contraindications of biological treatments

| | Adalimumab | Etanercept | Infliximab | Ustekinumab |
|---|---|---|---|---|
| Cardiac insufficiency (III or IV) | Yes | Yes | Yes | No |
| Active chronic infections including TB or HBV | Yes | Yes | Yes | Yes |
| Pregnancy or nursing | Yes | Yes | Yes | Yes |
| Known hypersensitivity to mouse proteins | No | No | Yes | No |

**Table 137.2** Important relative contraindications of biological treatments

| | Adalimumab | Etanercept | Infliximab | Ustekinumab |
|---|---|---|---|---|
| Demyelinating diseases | Yes | Yes | Yes | No |
| Malignancy (with the exception of BCC) and lymphoproliferative diseases or history of such disease | Yes | Yes | Yes | Yes |
| Use of live vaccines | Yes | Yes | Yes | Yes |
| Autoimmune diseases | No | No | Yes | No |
| HIV or AIDS | No | No | Yes | No |

### Laboratory Parameters

The laboratory parameters include the following exams:

- Full blood count
- Biochemical analysis (including liver enzymes, creatinine, uric acid, cholesterol, triglycerides, glucose)
- ESR/CRP
- Urine analysis
- Pregnancy test (urine)
- Hepatitis B (HBsAg, anti-HBs, anti-HBc) and C screening
- ANA/anti-dsDNA
- Mantoux test and/or QuantiFERON® Gold test

### Imaging

The imaging should include the following:

- Chest X-ray (in order to exclude active or latent tuberculosis)

In case of latent tuberculosis, the patient is not necessarily excluded from the biological treatments. A specialist needs to be consulted and the patient put under prophylactic anti-TB treatment prior to the beginning of biologics. The time of the prophylactic therapy varies according to the drugs used.

### Patient's Follow-Up

During treatment, it is very important to monitor the efficacy and safety of the therapy.

Clinical and standard laboratory evaluation needs to be repeated more closely during the beginning of the treatment (after 2 and 6 weeks for infliximab and after 4 weeks for adalimumab, etanercept, and ustekinumab) and then every 2–3 months following the administration schedule of each drug.

Chest X-ray, Mantoux skin testing and/or QuantiFERON® Gold test, and hepatitis B and C and HIV screening should be repeated once a year. Nevertheless we need to take into consideration that further specific testing might be needed according to clinical signs, risks, and exposure of each patient. Moreover, there may be some conditions that may require a more frequent laboratory monitoring. The most common of these conditions are the following:

- Presence of comorbidities
- Contemporary administration of prophylactic therapy for tuberculosis
- Contemporary administration of other systemic conventional drugs for psoriasis (methotrexate, retinoids, cyclosporine)
- Exacerbation and/or persistence of the disease

During treatment, it is also recommended to advise the patient to undergo regular cancer screening exams according to his age, sex, and family history (pap test, mammography for women, PSA for men).

## Efficacy and Long-Term Treatment with Biologics

All biological therapies have shown a rather fast onset of action, and the clinical improvement is usually visible within the first 4–8 weeks of treatment. The time of evaluation of their efficacy varies from 10 weeks of infliximab to 16 weeks in case of adalimumab and ustekinumab and 24 weeks of etanercept. More detailed information on their efficacy is shown in Table 137.3.

Regarding the long-term data on psoriasis therapy, their analysis is limited mostly due to different clinical trial designs and statistical methodology used for their interpretation. Adalimumab showed (REVEAL study) that the patients who had achieved a PASI 75 response at weeks 16 and 33 maintained that response for 100 weeks in 83 % and for 160 weeks in 76 % of the patients.

Etanercept in a post hoc analysis that included patients treated with different doses over a period of up to 4 years showed that 67 % of the patients that had a good response during the induction period (PGA 0/1) maintained the response at 24 weeks and showed only a slight variation through week 48.

Infliximab has no data of open-label extension trials available. In the EXPRESS II study, 71 % of the patients maintained PASI 75 until week 50 of continuous treatment.

**Table 137.3** Efficacy of different biological agents

| Therapeutic agent | Dose | PASI 75/(week 12) (%) | PASI 75/(6 months) (%) |
|---|---|---|---|
| Etanercept | 2×25 mg/week | 34 | 44 |
| Etanercept | 2×50 mg/week | 49 | 59 |
| Ustekinumab | 45 mg/12 weeks (body weight <100 kg) | 67 | 70 |
| Ustekinumab | 90 mg/12 weeks (body weight >100 kg) | 68–71 | 79 |
| Adalimumab | 40 mg/eow | 71–80 | 71 |
| Infliximab | 5 mg/kg | ≥80 | 82 |

| Biologic agent | Dosage | PASI 75 at week 12 (%) |
|---|---|---|
| Etanercept | 2×25 mg/week | 34 |
| Etanercept | *2×50 mg/week* | *49* |
| Ustekinumab | 45 mg/12 weeks (<100 kg BΣ) | *67* |
| Ustekinumab | 90 mg/12 weeks (>100 kg BΣ) | *68–71* |
| Adalimumab | 40 mg eow | *71–80* |
| Infliximab | 5 mg/kg | *≥80* |

Ustekinumab showed (PHOENIX I study) that 79 and 81 % for the doses of 45 and 90 mg, respectively, maintained their PASI75 at 5 years (244 weeks).

Given the good safety profile of the biologics, the therapeutic schema proposed is that of a continuous treatment, and treatment discontinuation is not advised with the exception of etanercept where also a discontinuous schema is also proposed.

According to the "new" for dermatology concept of treatment goals, a treatment is successful and should be continued if it results in a reduction of PASI ≥75 % or PASI ≥50 to <75 % combined with a DLQI ≤5. When the reduction in PASI is <50 % or PASI ≥50 to <75 % combined with a DLQI >5, treatment modifications should be considered. These treatment modifications include the following:

- Increase of drug dose
- Reduction of the intervals between drug doses
- Combination of therapies, either by adding topical treatment or a conventional systemic treatment (MTX, cyclosporine, acitretin)
- Change of the drug (usually done when all the above measures fail)

## New Biologics

In the last few years, a great progress has been achieved in identifying some of the risk genes for psoriasis leading to a better understanding of the pathogenetic pathways of the disease. This increased understanding of the immunogenetic pathways has led to the development of more targeted biological therapies. In fact, multiple new treatments are currently in development for the treatment of psoriasis and their preliminary data seem to be very promising.

**Table 137.4** Some of the new biological treatments currently under investigation for the treatment of psoriasis

| Class | Agent |
|---|---|
| Anti-TNF inhibitors | Certolizumab pegol |
| | Golimumab |
| | ART621 |
| Anti-IL23 | BI655066 |
| | SCH900222 |
| Anti-IL-17 | Brodalumab |
| | Secukinumab |
| | Ixekizumab |
| Anti-IL-20/22 | Fezakinumab |
| Phosphodiesterase 4 inhibitors | Apremilast |
| JAK inhibitors | Tofacitinib (JAK1/JAK3) |
| | Baricitinib (JAK1/JAK2) |
| | ASP-015K (JAK3) |

Among the new classes of targeted biological agents for psoriasis, the agents targeting the Th17/Il-23 axis will likely represent an important new therapeutic approach. These drugs by specifically targeting the IL-23/Th17 axis are likely to have a more targeted effect and an improved safety profile. Also the family of Janus kinases (JAK) inhibitors as well as the phosphodiesterase 4 inhibitors seems to show promising preliminary results.

An overview of some of the new biological treatments is shown in Table 137.4.

## Conclusions

Psoriasis is a chronic systemic inflammatory disease with a complex pathogenetic mechanism that involves interactions between the innate and adaptive immune systems, genes, and environment. Being a systemic inflammatory disease, psoriasis is associated with a number of comorbidities that include psoriatic arthritis, cardiovascular disease, metabolic syndrome, and depression. In addition, psoriasis is also associated with a significant impairment of quality of life, as it affects relationships, social activities, work, and emotional well-being. Moreover due to the chronic nature of the disease, often treatment options can be limited either because of their efficacy or because of their safety.

The introduction of the biological agents, such as adalimumab, etanercept, infliximab, and ustekinumab, has provided dermatologists with more options for the short- and long-term treatment of patients with psoriasis. With the use of biological therapies, it is now possible to achieve and maintain effective disease control with a good safety profile in the long term compared to the conventional treatments. Nevertheless, the careful screening and regular follow-up of the patients that undergo biological treatments are of great importance in order to avoid side effects and guaranty the patient efficacy and safety in the long term.

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