

Current therapeutic options in psoriasis

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Abstract. Psoriasis is a chronic inflammatory skin disorder, affecting the population worldwide. The exact etiology of the disease remains unknown, but there is a genetic predisposition, associated with a series of immunological determinants and predisposing environmental factors, which all lead to the characteristic erythematous-squamous skin lesions. These are visible, stigmatizing, with an important impact on the patients' quality of life. Common therapies for the treatment of psoriasis include various approaches such as topical, systemic, novel molecules, phototherapy, natural compounds and their combination. Topically used agents include dermatocorticoids, cignolin/dithranol, tars, vitamin D analogues and retinoids. Systemically used agents include methotrexate, cyclosporine and retinoids. These agents have a number of potential problems, such as limited in efficacy, organ toxicity, carcinogenic and broadband immunosuppression. Newer options for moderate to severe cases include biologic therapies, which are reported to have increased efficacy and fewer side effects. Currently, Infliximab, Adalimumab, Etanercept and Ustekinumab are approved for the treatment of psoriasis, and others molecules are at clinical stage. Despite the large array of therapies for psoriatic, none are curative. Physicians should be aware of all alternatives for a proper management of the disease.

Key Words: psoriasis, topical treatment, biologic agents

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Introduction

Psoriasis is a chronic skin disorder, characterized by inflammatory and hyperproliferative processes. Globally, reports on the prevalence of psoriasis reveal major differences in terms of ethnicity and climate zone, ranging between 0 and 11.8% (Jacobson et al 2011). In Europe, psoriasis affects approximately 2-3% of the population. Psoriasis onset can occur at any age, including birth, but there are two peaks, one in teenagers, around 15-20 years of age, and another in the elderly, 55-60 years of age. There are no significant differences in the incidence of psoriasis in male and female patients (Parisi et al 2013).

In most cases, the diagnosis of psoriasis is a clinical one, the careful examination evaluating the characteristic appearance of the lesions (fig. 1), their typical localization predominantly on the extensor surfaces and family history of psoriasis are highly suggestive, allowing easy diagnosis (Langley et al 2005).



Fig.1 Psoriasis vulgaris

Etiopathogenesis of psoriasis is a complex and not yet fully elucidated genetic predisposition, being associated with a series of immunological determinants and predisposing environmental factors, working together to produce a clinical chart characterized by the presence of characteristic erythematous-squamous skin lesions (Lowe et al 2007; Griffiths et al 2005). (fig.2) These are easy to notice, thus stigmatizing, with a significant impact on the patients' quality of life (Finlay et al 1995).

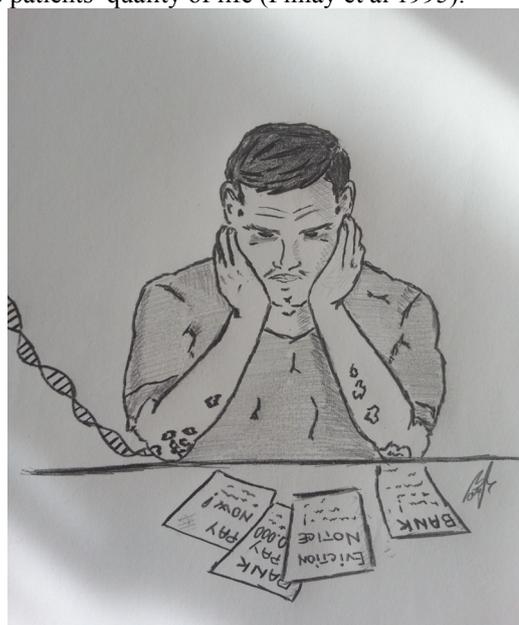


Fig.2. Psoriasis etiopathogenesis

Additionally to all these aspects, the treatment of psoriasis, through its chronic nature, variable efficiency and well-known side effects, represents an additional problem for these patients (Richards et al 2001).

General therapeutic measures

The treatment of psoriasis is lengthy, most patients requiring life-long therapy. It varies depending on the clinical type and severity of disease. The therapeutic approach must be individualized based on the spread of the disease, the anatomical location, the impact on quality of life, the possible coexistence of psoriatic arthritis, as well as the patient's compliance with the treatment. The following are indicated as general measures: avoid stress, alcohol consumption, certain medications (beta-blockers, lithium, antimalarials, etc.), reduce the amount of sweets and fats in the diet, annual heliomarine therapy, maintain good hydration by drinking adequate amounts of liquid and apply emollients. A very close doctor-patient relationship is also essential. Genetic counseling considers contraception only when both parents suffer from psoriasis (Christophers et al 2009).

Topical therapy

Mild forms of psoriasis, affecting less than 3% of the body surface area, respond to topical application of agents selected based on the appearance of the lesions. In the case of thick laminated scales, it is first necessary to uncover the lesion, to allow the applied medication to penetrate it. This can be accomplished by applying keratolytic agents such as 1-5% salicylic acid or 5-15% urea.

Subsequently, it is indicated to use topical agents such as gels, creams, lotions, ointments, sprays or foams, which can be used by themselves or as occlusive dressing, thereby increasing their effectiveness.

The most commonly prescribed agents are dermatocorticoids, whose anti-inflammatory potency varies depending on the chosen formulation, thus being classified into four classes, from hydrocortisone, which is the weakest, to clobetasol, which is the strongest. They are not free from the risk of local adverse effects (telangiectasia, skin atrophy, purpura, hirsutism) or systemic adverse effects (for chronic use). To prevent side effects, guidelines indicate a maximum dose of 50g/week, for up to two weeks (Mason et al 2002; Bruner et al 2003).

Other topical preparations used are cignolin/dithranol (reduce symptoms), tars, vitamin D analogues (calcipotriol, tacalcitol - induce terminal differentiation and reducing hyperproliferation of keratinocytes), retinoids (tazarotene - normalizes aberrant keratogenesis), calcineurin inhibitors (tacrolimus, pimecrolimus - anti-inflammatory effect), UVB phototherapy, PUVA photochemotherapy or RePUVA (Lowes et al 2007).

Systemic medication

When topical treatment fails to control the disease, in mild forms (affecting 3-10% of the skin) or severe forms (affecting more than 10% of the body surface) of psoriasis, it is necessary to associate it with systemic therapy.

The most frequently used agents are methotrexate, cyclosporine and retinoids (vitamin A derivatives: etretinate-Tigason and acitretin-Neotigason).

Methotrexate is a folic acid antagonist that interferes with purine synthesis and thus inhibits DNA synthesis and cell replication. In addition to the anti-mitotic effect, it has a specific activity of T cell suppression and, in low dose, methotrexate has anti-inflammatory and antiproliferative effects.

It is indicated in moderate to severe forms of psoriasis, as well as in psoriatic arthritis. It can be administered orally or by injection, in a single weekly dose, or in more doses, given after a 2.5-5 mg test dose. The weekly dose range (7.5 to 22.5 mg) depends on the clinical response. When the desired effect is obtained, the dose is gradually reduced to about 2.5 mg a month. Folic acid is added to the treatment to prevent macrocytic anemia, oral stomatitis and to reduce gastrointestinal symptoms. Since methotrexate can have severe adverse effects, it is required to carefully select and monitor patients. The risk of bone marrow suppression requires blood count exams every 1-3 months. A number of concomitant medications may increase the risk of bone marrow suppression, for example the use of sulfonamides and their derivatives. Rare complications of systemic therapy are pulmonary fibrosis, liver fibrosis and cirrhosis. Due to the risk of teratogenic effects, methotrexate is absolutely contraindicated in pregnancy, being indicated to stop using it three months before conception.

Another effective agent used in psoriasis treatment is cyclosporine, a macrocyclic immunosuppressant that specifically inhibits helper T cell and keratinocyte activation and proliferation. The recommended starting dose is of 2.5 mg/kg/day, titrated every 2-4 weeks according to patient response, up to a maximum of 5 mg/kg/day. Cyclosporine requires renal function and blood pressure monitoring, due to the increased risk of nephrotoxicity and hypertension. Other possible side effects include hyperkalemia, dyslipidemia, hypomagnesemia, hypertrichosis, gastrointestinal and neurological disorders.

Oral retinoids (vitamin A derivatives) are another useful option in the treatment of psoriasis. These synthetic hormones mount on nuclear retinoid receptors, thereby altering the transcription process, resulting in hyperproliferation of keratinocytes, affecting their differentiation.

Acitretin monotherapy begins with a dose of 10-25 mg, which is further adjusted based on patient response. The side effects are similar to those observed with hypervitaminosis A and can lead to dry skin, cheilitis, conjunctivitis, and hair loss. It can also induce dyslipidemia, skeletal abnormalities, ligament calcification or osteoporosis. The risk of teratogenic effects resulting from the use of retinoids is high and therefore, contraception is indicated throughout treatment, as well as 3 years after its cessation (Griffiths et al 2000).

Biological agents

The above mentioned conventional treatment options are linked to well-known adverse effects and in many cases, they have limited effectiveness over time. These shortcomings have led to the introduction of a new therapeutic tool for moderate and severe forms of psoriasis, biological agents. Currently, they are reserved for cases of psoriasis unresponsive to other therapies or with contraindications to conventional systemic therapies. Biological therapies have been used worldwide in the treatment of severe forms of autoimmune diseases (rheumatoid arthritis, ankylosing spondylitis, Crohn's disease) for about 17 years.

Based on the key role of T lymphocytes and multiple proinflammatory cytokines in psoriasis, the opportunity of administrating certain biological agents in this pathology has been examined. Thus, since 2003, a number of biologic therapies have entered the current therapeutic arsenal of psoriasis.

The effectiveness of biological agents is based on the action of certain fusion proteins, recombinant proteins or monoclonal antibodies, thus conferring the advantage of a selective immunological activity. From a clinical point of view, these agents cause remission of existing lesions and prevent the appearance of new lesions.

Depending on their therapeutic target, biological agents can be divided into two classes: anti-TNF α (fig. 3) and anti-IL12/23 antibodies (fig. 4).

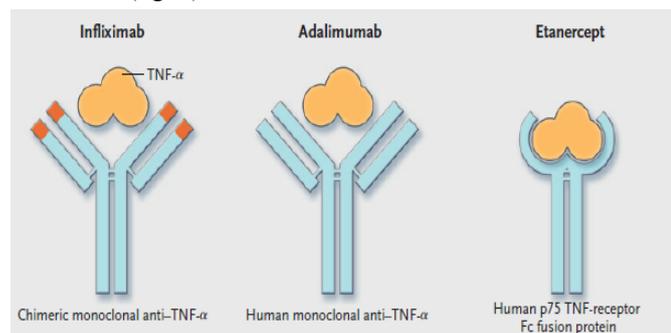


Fig. 3 Anti -TNF α biological agents

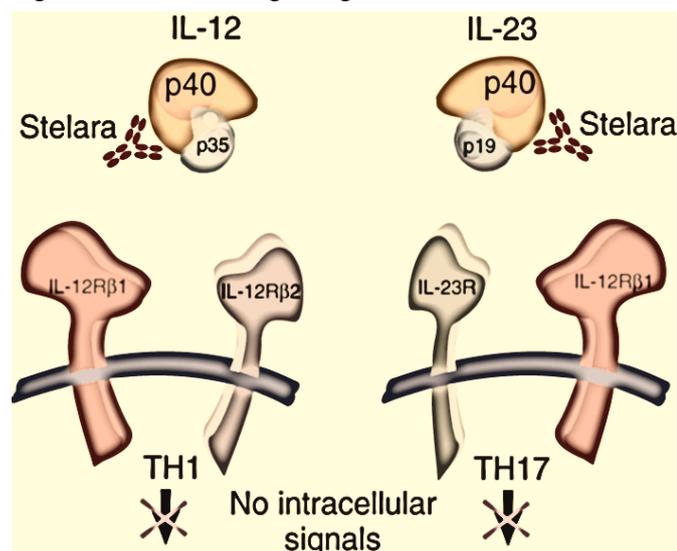


Fig. 4 Mechanism of action of Ustekinumab (Stelara)

The following preparations are approved by relevant factors for use in the treatment of moderate to severe psoriasis: Infliximab, Adalimumab, Etanercept, and Ustekinumab.

Infliximab (Remicade) is a mouse/human chimeric monoclonal IgG1 antibody produced by recombinant DNA technology that binds to TNF α , neutralizing its activity. The product is available as lyophilized powder, which is administered by intravenous infusion at a dose of 5 mg/kg for 2-3 hours, at weeks 0, 2 and 6, and every 8 weeks thereafter. In time, there is a risk of reduction and even total loss of efficiency due to the formation of anti-infliximab antibodies. This risk has also been reported during etanercept and adalimumab therapy (Gottlieb et al 2004). Adalimumab (Humira) is a recombinant, fully human monoclonal antibody expressed in Chinese hamster ovary cells. It is

administered subcutaneously at a dose of 40 mg (prefilled syringe) once every two weeks, being useful for both skin manifestations and psoriatic arthritis (Menter et al 2008).

Etanercept (Enbrel) is a fusion protein produced by coupling human TNF α receptor p75 to the Fc domain of human IgG1. The protein is produced by recombinant DNA technology within a Chinese hamster ovary cell expression system. It is administered subcutaneously by the physician, or directly by the patient, at a dose of 25 mg (prefilled syringe), twice a week. Etanercept is also effective in psoriatic arthritis, improving the symptoms of fatigue and depression of patients with psoriasis (Mease et al 2000).

Ustekinumab (Stelara) is a fully human monoclonal IgG1k antibody produced on murine cells, binding with high specificity to the p40 subunit common to the IL-12 and IL-23 cytokines. Therefore, it blocks binding of interleukins to IL-12R β 1 receptor protein, common for their receptors. The treatment is injected subcutaneously, 45 mg (vial or prefilled syringe) at week 0, 4 and every 12 weeks thereafter. For patients weighing over 100 kg, the dose is double (90 mg). Its efficiency and safety are supported by Phase III trials (PHOENIX 1 and PHOENIX 2) and more recently, by ACCEPT clinical trial (Giunta et al 2010).

The benefits of the treatment with biological agents are significant, the increased efficiency and the achievement of long periods of remission, as well as the convenient administration, are essential for improving patients' quality of life.

However, the response to biological agents is not always optimum. Some cases have even been aggravated as a result of their administration. In addition, long-term toxic effects are only partly known. One of the medications, Efalizumab, has already been withdrawn from the market due to its adverse effects (progressive multifocal leukoencephalopathy) occurring after obtaining marketing approval. Other limitations are related to the formation of anti-agent antibodies and the cost of these treatments, biological agents being extremely expensive. All these reasons call for a rigorous selection of the patients who can safely benefit from this therapeutic approach, following well defined criteria (Di Lernia 2010).

Other therapeutic options

Up to 50% of patients with psoriasis choose to use non-medical preparations, such as those containing natural substances. The choice is in many cases motivated by the fear of side effects of conventional medication, as well as by the insufficient control of the disease. These preparations are used alone or in combination with the medication prescribed by the physician, who is not always well informed about their use. The most frequently used are preparations containing aloe vera, capsaicin, chamomile, indigo naturalis and Mahonia aquilifolium. There are still few scientific studies in this direction, but they are consistent regarding the anti-inflammatory and antiproliferative effects of these preparations (Bhuchar et al 2012; Deng 2013).

Psychosocial aspects

Despite the multiple therapeutic options, in most cases, disease control is only partial, quality of life of patients being significantly affected by the persistence or recurrence of skin lesions, a source of permanent discomfort and anxiety, as well as by the chronic treatment they are forced to follow.

Outlook

A series of new therapeutic agents are currently in various phases of clinical trials. There are studies on new oral and injected systemic options, as well as topical medications (fig. 5). Eight of these agents are already in Phase III clinical trials and will probably enter the current therapeutic arsenal very soon.



In order to provide effective treatment to patients, it is essential to know all treatment options, with the indications, advantages and limitations specific to each type of medication.

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Citation Boca AN, Badalica-Petrescu M, Buzoianu AD. Current therapeutic options in psoriasis. HVM Bioflux 2014;6(1):6-10.

Editor Ștefan C. Vesa

Received 3 January 2014

Accepted 24 January 2014

Published Online 24 January 2014

Funding None reported

**Conflicts/
Competing
Interests** None reported