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REVIEW

Biological therapies in psoriasis - revisited

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Psoriasis is a chronic, immune mediated disorder affecting approximately 2% of the population. Even in our days, patients with psoriasis are confronted with stigmatization and social rejection. As a result, their quality of life is significantly impaired. Biological therapies have revolutionized the treatment of moderate to severe psoriasis. The aim of this paper is to look over the most important biological therapies available for the management of plaque-type psoriasis.

Key words: psoriasis, biological therapies, TNF-α, IL-17, anti-IL-12/23.

INTRODUCTION

Psoriasis is a chronic, immune-mediated skin disorder with a worldwide occurrence, affecting approximately 2% of the population. It has a polygenic predisposition. Environmental factors like trauma, infections or medications can trigger the eruption of psoriasis. It is clinically characterized by erythematous, well demarcated plaques covered by silvery-white scales, most often affecting the extensor areas of the extremities, the scalp and the lower lumbosacral area. However, any area can be involved. The disease can occur at any age but two peaks in age of onset were recognised: one between 20 and 30 years and the second between 50 and 60 years. Almost 90% of patients have plaque-type psoriasis [1-3].

The pathogenesis of psoriasis is not completely understood. It was initially considered an epidermal disease and several mediators like cyclic AMP, protein kinase C, phospholipase C, eicosanoids, transforming growth factor-α (TGF-α) were incriminated. In recent years however it has been regarded as a T-cell driven disease and the role of lymphocytes and cytokines was intensely studied [4, 5]. Th1 cells produce IFNγ, TNFα and TNFβ while Th17 cells produce IL-17, IL-21 and IL-22. IL-17 has an important role in neutrophil chemotaxis and angiogenesis while IL-22 determines hyperproliferation of keratinocytes. IFNγ increases the production of IL-23 in dendritic cells which expands Th17 and Th22 cells. TNFα is a pro-inflammatory cytokine which facilitates the entry of inflammatory cells in the psoriatic plaque by inducing adhesion molecules on vascular endothelial cells. It also stimulates keratinocytes production and activates macrophages and dendritic cells. Other cells also produce cytokines with an important role in the pathogenesis of psoriasis. Therefore, keratinocytes produce IL-8, IL-12, IL-15, IL-18 and TNFα while dendritic cells produce IFNα, TNFα, IL-20 and IL-23. The interaction of all these cytokines is believed to determine the appearance of the psoriatic plaque [1, 4].

The burden of disease is significant in patients with psoriasis. Even in our days, patients with psoriasis are confronted with stigmatization and social rejection. The incidence of mood disorders like depression and anxiety in those patients is higher than in general population. The quality of life is also significantly impaired due to the constant need of treatment, hospitalizations, missed work days, itching and interference with daily activities, among others [6-9].

The treatment of psoriasis has evolved a lot over the years. In 1500 BC, before psoriasis was recognized as a separate entity, cat and dog's dung, mixtures of onions, salt and urine or wasp's dung in milk of sycamore were considered appropriate treatments for skin disorders. In the 19th century psoriasis was treated with arsenic, mercury, alkaline salts, phosphorus, thyroid extracts and salicylates [10]. In our days patients with psoriasis have several treatment options for topical or systemic use. Conventional treatments for psoriasis include topical corticosteroids, topical retinoids, vitamin D analogs, dithranol, tars, salicylic acid, phototherapy,

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methotrexate, acitretin and cyclosporine A. Non-compliance to therapy is however often encountered because of the messiness associated with applying topical treatments, the limited efficacy of all agents and the high rate of adverse events. Under those circumstances, the identification of new therapies for psoriasis was of utmost importance [11].

BIOLOGICAL THERAPIES

Biological therapies revolutionized the treatment of plaque psoriasis. Advances in molecular technology as well as a better understanding of the pathogenic mechanisms in psoriasis allowed the development of more targeted treatments (Table 1).

Table 1
Biological agents for psoriasis [1, 12, 27, 46, 49, 53, 64]

Class	Drug	Target	Administration	Dosing regimen in psoriasis
T-cell modulators	Alefacept (Amevive®)	CD2 receptor on T cells	i.m	15 mg/week for 12 weeks. 12 weeks pause. Multiple 12 weeks courses are possible
	Efalizumab (Raptiva®)	CD11a subunit of LFA1	s.c	1 mg/kg weekly.
TNF antagonists	Etanercept (Enbrel®)	TNF-α	s.c	25 mg or 50 mg twice weekly
	Adalimumab (Humira®)	TNF-α	s.c	80 mg loading dose followed by 40 mg every 2 weeks
	Infliximab (Remicade®)	TNF-α	i.v	5 mg/kg at weeks 0, 2, 6 and every 8 weeks thereafter
Anti-IL biologic agents	Ustekinumab (Stelara®)	P40 subunit of IL12 and IL23	s.c	45 mg for patients who weigh< 100 kg and 90 mg for patients who weigh > 100 kg at weeks 0, 4 and every 12 weeks thereafter
	Sekukinumab (Cosentyx®)	IL17A	s.c	300 mg at weeks 0, 1, 2, 3, 4 and every 4 weeks thereafter
	Ixekizumab (Taltz®)	IL-17A	s.c	160 mg at week 0; 80 mg at weeks 2, 4, 6, 8, 10, 12 and 80 mg every 4 weeks thereafter.
JAK kinase inhibitors	Tofacitinib (Xeljanz®/Jakvinus)	JAK 1 and JAK 3 inhibitor	oral	Under investigation for psoriasis
Phosphodiesterase inhibitors	Apremilast (Otezla®)	PDE4	oral	30 mg/week

Abbreviations: TNF – tumor necrosis factor; LFA – Lymphocyte function-associated antigen; SRCR-D1 – scavenger receptor cysteine-rich domain 1; JAK – Janus kinase; IL – interleukin; PDE4 – Phosphodiesterase 4; i.m – intramuscular; i.v – intravenous; s.c – subcutaneous.

T cell modulators

Alefacept

Alefacept was the first targeted immune modulator specifically designed for the treatment of chronic plaque psoriasis. It was approved by the Food and Drug Administration (FDA) in 2003 for moderate to severe plaque psoriasis. In Europe, it was approved only in Switzerland in 2004.

Alefacept is a human fusion protein composed of the extracellular CD2-binding portion of the human leukocyte function antigen-3 (LFA-3) and the Fc portion of human IgG1 [2, 11, 12]. It inhibits T cell activation by binding to the CD2 receptor on T lymphocytes and blocking the interaction between LFA-3 expressed on antigen presenting cells and CD2 expressed on T cells. It also induces apoptosis in memory T cells by binding of the IgG1 portion to the CD 16 receptor of NK cells [1, 11, 13-15].

Alefacept is administered at doses of 15 mg intramuscularly once weekly for 12 weeks followed by a 12 weeks period without treatment. Multiple 12 weeks courses are possible in responders. Studies showed that alefacept was superior to placebo in psoriasis patients. PASI 75 was obtained in approximately 30% of patients after one course of treatment with alefacept. In the 12 weeks follow-up period 71% of patients maintained at least PASI 50. Multiple courses of treatment are associated with better results [2, 16-18].

Studies showed that Alefacept is generally safe and well tolerated. The most frequent side effects are mild headache and injection site inflam-

mation and pain. Increased transaminase levels and hepatitis were rarely reported. Anti-alefacept antibodies are present in up to 4% of patients but they are non-neutralizing and were not correlated with adverse reactions [17, 18].

In 2011 the promotion and distribution of alefacept was stopped. This event was not related to any safety concerns [15].

Efalizumab

Efalizumab is a recombinant humanized monoclonal IgG1 antibody directed against CD11a, the alpha subunit of the leukocyte function associated antigen-1 (LFA-1). LFA-1 interacts with intercellular adhesion molecule-1 (ICAM-1) located on antigen presenting cells and endothelial cells thus promoting T-cell activation and migration to the skin. Efalizumab therefore prevents T cell activation and migration to activation sites which are important steps in the pathogenesis of psoriasis [2, 11, 12, 19].

Efalizumab was approved by the FDA in 2003 for the treatment of moderate to severe plaque psoriasis. In 2004, it was also approved in Europe by the European Medicines Agency (EMA) [11]. Gordon *et al.* performed a double-blind, placebo controlled trial in which they included 556 patients with moderate to severe psoriasis, 369 of whom received subcutaneous efalizumab and 187 received placebo. The authors found that efalizumab was superior to placebo on all end points. PASI 75 was achieved in 27% of patients treated with efalizumab and in only 4% of patients in the placebo group [20].

Efalizumab was administered at doses of 1 mg/kg weekly for 12 weeks. Patients who achieved at least PASI 50 were candidates to continue the treatment [11].

Efalizumab was voluntarily withdrawn from the market in 2009 in Europe and in the USA after three cases of progressive multifocal leukoencephalopathy (PML) occurred in patients receiving this drug. PML is a fatal demyelinating central nervous system disease caused by the infection with John Cunningham polyomavirus (JCV). This opportunistic infection was previously associated with AIDS and various malignancies. In recent years, it has been linked to immunomodulating therapies like mycophenolate mofetil, rituximab, natalizumab and efalizumab. The psoriatic patients who developed PML had been treated with efalizumab for more than three years. When the drug was taken off the market, more than 46000 patients had received efalizumab [21-23].

TNF-α antagonists

Etanercept

Etanercept is a fully human soluble dimeric fusion protein consisting of the extracellular domain of the TNF-α receptor linked to the constant region (Fc) of human IgG1. Etanercept prevents the interaction between TNF-α and its cell surface receptors and therefore inhibits its activity. It was approved in 2004 for the treatment of moderate to severe psoriasis in patients who have not responded to conventional systemic therapies or who have contraindications or do not tolerate those [1, 2, 11, 24].

Etanercept is administered subcutaneously at a dose of 25 mg twice weekly or 50 mg twice weekly for 12 weeks. The maintenance dose is 50 mg weekly or 50 mg twice weekly [2, 11].

Leonardi *et al.* performed a study on 672 patients with chronic plaque psoriasis to evaluate the safety and efficacy of different regimens of etanercept. 652 of those were randomized to receive placebo, low dose etanercept (25 mg/week), medium dose etanercept (25 mg twice weekly) or high dose etanercept (50 mg twice weekly). An improvement of 75%, as measured by PASI (PASI75) was found in 4% of patients receiving placebo, 14% of patients receiving low dose etanercept, 34% of patients receiving medium dose etanercept and 49% of patients receiving high dose etanercept, after 12 weeks of treatment. The authors also found that etanercept was well tolerated [25].

Fernández-Torres *et al*. performed a study in which they aimed to evaluate the long-term response to etanercept monotherapy in daily practice. The authors included in the study 72 adult patients who achieved an improvement of at least 50% after 12 weeks of treatment. The authors found that PASI 75 was achieved in 50% of patients after 3 months, 62.8% of patients after 6 months, 52.4% after 12 months, 46.7% after 24 months, 5.9% after 36 months and 5.9% after 42 months. The authors concluded that the maximum response to etanercept treatment is obtained between 6 and 9 months and remains stable in 50% of patients until 18-24 months [26].

Etanercept is also approved for the treatment of children and adolescents with severe chronic plaque psoriasis from the age of 6 years who failed to respond or are intolerant to conventional treatments. The recommended dose is 0.8 mg/kg administered weekly (maximum 50 mg per dose) [27].

Paller *et al*. assessed the efficacy and safety of etanercept in children and adolescents aged 4 to 17 years old with psoriasis. 211 patients were initially randomized to receive etanercept or placebo. After 12 weeks 57% of patients receiving etanercept and 11% of those in the placebo group achieved PASI 75. All patients were then treated with etanercept for 24 weeks. At week 36, 68% of patients treated with etanercept and 65% of patients who initially received placebo achieved PASI 75. In the last 12 weeks patients were randomly assigned to receive placebo or etanercept. 42% of patients who received placebo lost the response. 80% of patients receiving etanercept achieved PASI 75 at week 48. All adverse events resolved without sequelae. The authors concluded that etanercept is efficient in children and adolescents with moderate to severe psoriasis [28].

Studies show that etanercept is relatively safe in the short term [11]. Injection site reactions are the most common adverse events and are usually mild. Upper respiratory tract infections are also more frequent in patients receiving etanercept. Reactivation or primary infection with *Mycobacterium tuberculosis* is rare [11, 29].

Anti-etanercept antibodies were detected in the serum of less than 5% of patients and they were non-neutralizing; they were not associated with decreased drug response or adverse reactions [29].

Adalimumab

Adalimumab is a fully human recombinant IgG1 monoclonal antibody targeting TNF-α. It binds to both soluble and cell-bound forms of TNF-α thus inhibiting its action. It was approved for the treatment of plaque psoriasis in 2007 [1, 2].

Adalimumab is administered subcutaneously at an initial, loading dose of 80 mg and a maintenance dose of 40 mg every two weeks [11].

Gordon *et al*. showed in a study published in 2006, in which 147 patients with moderate to severe psoriasis were included, that adalimumab was superior to placebo (PASI 75 at week 12 in 53% of patients who received adalimumab every 2 weeks *versus* 4% of patients in the placebo arm) [30]. Menter *et al*. conducted a randomized, placebo controlled trial in which they aimed to assess the efficacy and safety of adalimumab in continuous versus interrupted therapy. At week 16, 71% of patients treated with adalimumab and 7% of those who received placebo achieved PASI 75. Between weeks 16 and 33 all patients who achieved PASI 75 received adalimumab. At week 33, patients who maintained PASI 75 and were initially treated with adalimumab were randomized to receive adalimumab or placebo until week 52. At week 52, 28% of patients who were re-randomized to placebo and 5% of patients who received continuous adalimumab treatment failed to achieve adequate response [31]. In 2008 Saurat *et al*. performed a study in which they aimed to compare the efficacy and safety of adalimumab with that of methotrexate and placebo. At week 16, PASI 75 was achieved by 79.6% of patients receiving adalimumab, 35.5% of patients receiving methotrexate and 16.7% of those receiving placebo. Adverse events were similar in the three groups and the authors concluded that adalimumab was superior to methotrexate and placebo [32].

Papp *et al*. assessed the efficacy and safety of adalimumab *versus* methotrexate in children and adolescents with moderate to severe psoriasis. 114 patients were randomized to receive 0.8 mg/kg adalimumab, 0.4 mg/kg adalimumab or methotrexate. At week 16, 58% of patients receiving 0.8 mg/kg adalimumab, 44% of patients receiving 0.4 mg/kg adalimumab and 32% of those receiving methotrexate achieved PASI 75. The authors concluded that patients who received 0.8 mg/kg adalimumab obtained significant improvements in PASI 75 as compared to those who received methotrexate [33].

Even though adalimumab is a completely human antibody, anti-drug antibodies have been described in the medical literature and have been associated with loss of efficacy [2]. Carrascosa *et al*. showed in a study published in 2017 that there is a correlation between drug serum levels and clinical efficacy as measured by PASI score [34].

Adalimumab is generally considered a safe treatment. The most frequently reported adverse event is injection site reaction which occurs in approximately 20% of patients. Infections are also frequently reported, especially upper respiratory infections and rhinitis. Occasional cases of tuberculosis were also reported. Appropriate screening before starting adalimumab treatment and during treatment is therefore mandatory. Hepatotoxicity, drug induced lupus and lymphoma were also very rarely reported [2, 11, 35].

Infliximab

Infliximab is a monoclonal chimeric IgG1 antibody composed of a human antibody constant region and murine variable regions. It targets both soluble and membrane-bound TNF-α. It was approved by EMA in 2005 for the treatment of moderate to severe psoriasis [1, 11, 15, 36].

Infliximab is administered at a dose of 5 mg/kg body weight as an intravenous infusion over 2 hours at weeks 0, 2, 6 and every 8 weeks thereafter [1, 11].

The efficacy of infliximab is supported by several studies. Reich *et al*. performed a double-blind study in which they aimed to assess the efficacy and safety of infliximab. 378 patients were randomized to receive infliximab 5 mg/kg or placebo. After 24 weeks, all patients crossed over to infliximab. At week 10, 80% of patients receiving infliximab and 3% of those in the placebo group achieved PASI 75. The treatment was well tolerated [37]. Menter *et al*. performed a study on 835 patients with moderate to severe psoriasis to compare the efficacy of continuous and intermittent infliximab maintenance regimens. The patients were randomized to receive 3 mg/kg infliximab, 5 mg/kg infliximab or placebo for 14 weeks. At week 14 patients who received infliximab were re-randomized to continuous or intermittent treatment. The authors found a 75% improvement in 75.5% of patients receiving 5 mg/kg infliximab, 70.3% of patients receiving 3 mg/kg infliximab and 1.9% of those in the placebo group, at week 10. At week 50, PASI 75 was achieved in 44% of patients receiving 3 mg/kg and 55% of patients receiving 5 mg/kg of infliximab in continuous treatment and 25% of patients receiving 3 mg/kg and 38% of patients receiving 5 mg/kg infliximab in the intermittent group. The authors found that infliximab was generally well tolerated [38].

Infliximab is also associated with a significant improvement in the quality of life. Feldman *et al.* showed, in a study performed on 249 patients with severe plaque psoriasis, that the quality of life, as measured by Disease Life Quality Index (DLQI), is improved by 84% in patients receiving 3 mg/kg infliximab, 91.0% in patients receiving 5 mg/kg infliximab and 0% in patients receiving placebo after 10 weeks of treatment [39].

Since infliximab is a chimeric antibody there is some concern regarding the occurrence of neutralizing anti-infliximab antibodies. These antibodies are associated with lower drug concentrations and the occurrence of adverse drug reactions. The occurrence of anti-infliximab antibodies was reported in disorders like Crohn's disease where it is associated with shorter duration responses but data regarding the appearance of anti-drug antibodies in patients with psoriasis is scarce. Some authors suggest that the combination with low-dose methotrexate improves the long-term efficacy of infliximab. Other authors consider that increasing the dose of infliximab in those patients who stop responding to treatment is more efficient than adding methotrexate [1, 11, 12, 36, 40].

Infliximab is generally well tolerated. Infusion-related adverse reactions are encountered in 16-20% of patients. Autoantibody formation may lead to the development of acute or delayed hypersensitivity reactions. Infections are frequently reported, especially upper respiratory infections. Occasionally infliximab was associated with mycobacterial infections or reactivation of latent tuberculosis. Opportunistic infections like histoplasmosis, aspergillosis, coccidioidomycosis or pneumocystosis were also reported [1, 11, 36].

Anti-interleukin biologic agents

a. IL12/IL23 inhibitors

Ustekinumab

Ustekinumab is a fully human IgG1 kappa monoclonal antibody directed against the p40 subunit of IL12 and IL23. By preventing IL12 and IL23 to bind to their receptors ustekinumab inhibits the T17 and Th1 signalling pathways [2, 4]. It was registered in 2009 for the treatment of moderate to severe psoriasis [11].

Ustekinumab is administered subcutaneously at a dose of 45 mg for patients who weigh less than 100 kg and 90 mg for patients who weigh more than 100 kg, at weeks 0, 4 and then every 12 weeks [2].

A randomized, double blind, placebo controlled study performed by Leonardi *et al*. on 766 patients with moderate to severe psoriasis who were randomized to receive ustekinumab 45 mg, ustekinumab 90 mg or placebo found that after 12 weeks of treatment 67.1% of patients receiving 45 mg ustekinumab, 66.4% of those receiving 90 mg ustekinumab and 3.1% of the ones in the placebo group achieved PASI 75. At week 40 patients who maintained an improvement of at least 75% were re-randomized to maintenance therapy or withdrawal. After 1 year, PASI 75 was better preserved in the group receiving maintenance therapy [41].

Papp *et al*. performed a double blind, placebo-controlled trial in which they included 1230 patients with moderate to severe psoriasis who were randomized to receive ustekinumab 45 mg, ustekinumab 90 mg or placebo. At week 12, 66.7% of patients receiving ustekinumab 45 mg, 75.7% of those receiving ustekinumab 90 mg and 3.7% of those in the placebo group achieved PASI 75. At week

28 patients who achieved PASI 50 but did not achieve PASI 75 were randomized to continue ustekinumab every 12 weeks or to escalate to ustekinumab every 8 weeks. At week 52, a good response was noticed only in those patients who received ustekinumab 90 mg every 8 weeks [42]. Further studies, in which patients treated with ustekinumab were followed for 5 years, showed no dose related or cumulative toxicity. The authors concluded that exposure for up to 5 years to ustekinumab is safe and effective [43, 44].

A study performed in 2010 by Griffiths *et al*. compared the efficacy and safety of ustekinumab 45 mg and 90 mg to that of etanercept (50 mg twice weekly). At week 12, 67.5% of patients receiving 45 mg of ustekinumab, 73.8% of those receiving 90 mg of ustekinumab and 56.8% of those receiving etanercept achieved PASI 75. The authors concluded that ustekinumab was superior to etanercept with regard to efficacy and has a similar safety profile [45].

Ustekinumab is generally well tolerated. Injection site reactions can occur. Patients must be screened for mycobacterial infection at the beginning of the treatment and every year during treatment. There is an increased risk of myocardial infarction and stroke. Injection site reactions were also reported. Nasopharyngitis and headache were the most common side effects [2, 46].

b. IL-17 inhibitors

Secukinumab

Secukinumab is a recombinant, fully human IgG1 kappa monoclonal antibody directed against IL-17A. It was approved by the FDA in 2015 for the treatment of moderate to severe psoriasis patients who are candidates for systemic therapy or phototherapy [47, 48].

Secukinumab is administered subcutaneously at a dose of 300 mg at weeks 0, 1, 2, 3, 4 and every 4 weeks thereafter [49].

The efficacy and safety of secukinumab in the treatment of psoriasis are supported by several studies. Papp *et al*. showed in a study published in 2013 that the efficacy of secukinumab 3 × 75 mg and secukinumab 3 × 150 mg is superior to placebo [50]. Four multicentre, randomized, double blind, placebo-controlled trials which included 2403 patients with psoriasis had a paramount importance in determining the efficacy and safety of secukinumab: ERASURE, FIXTURE, FEATURE and JUNCTURE. According to these studies, the maximum effect is achieved after 16 weeks of 300 mg secukinumab treatment and is maintained up to 52 weeks. Also, a 50% improvement is achieved from week 3 [48, 51, 52].

The most frequent adverse events reported in patients treated with secukinumab are diarrhoea, upper respiratory tract infection, mucocutaneous infections with candida. Pre-treatment evaluation for tuberculosis is mandatory [49, 52].

Ixekizumab

Ixekizumab is a recombinant humanized IgG4 monoclonal antibody which binds with high affinity to IL-17A. It was approved in 2016 by the FDA and EMEA for the treatment of plaque psoriasis in adults who are candidates for systemic therapy [53].

Ixekizumab is administered subcutaneously at a dose of 160 mg at week 0 and 80 mg at weeks 2, 4, 6, 8, 10 and 12. The maintenance dose is 80 mg every 4 weeks [53].

Three main studies support the efficacy and safety of Ixekizumab in psoriatic patients: UNCOVER-1, UNCOVER-2 and UNCOVER-3. 1296 patients were enrolled in the UNCOVER-1 study. The authors found that after 12 weeks of treatment ixekizumab administered every 2 weeks is superior to ixekizumab administered every 4 weeks and placebo (PASI 75 at week 12 89.1% *vs* 82.6% *vs* 3.9%). In the UNCOVER-2 study the researchers included 1224 patients who were randomized to receive placebo or ixekizumab 80 mg every 2 weeks or ixekizumab 80 mg every 4 weeks or etanercept 50 mg weekly for 12 weeks. The authors found that ixekizumab administered every 2 weeks was superior to ustekinumab every 4 weeks, etanercept and placebo (PASI 75 at week 12 89.7% *vs* 77.5% *vs* 41.6% *vs* 2.4%). In the UNCOVER-3 study 1346 patients were included. Superior results were also found for the 80 mg every 2 weeks regimen [53-56].

Gottlieb *et al*. showed in a study published in 2016 that the efficacy of ixekizumab is similar in patients who received prior treatment with biologicals and naive patients [57].

The most frequent adverse events are nasopharyngitis, upper respiratory tract infection, injection-site reaction, injection-site erythema and headache [54].

Small molecule inhibitors

Unlike biologicals, small molecule inhibitors target enzymes within signalling pathways. Several small molecules are being investigated for the treatment of psoriasis [58].

Janus kinase inhibitors

The Janus kinases (JAKs) are cytoplasmic tyrosine kinases which, after activation, phosphorrylate the signal of transducer and activator of transcription (STAT) proteins. This leads to transportation of the proteins in the nucleus to regulate gene expression. The JAK-STAT pathway is used by several cytokines to transmit signals to the nucleus. IL-12 and IL-23 are two very important cytokines in the pathogenesis of psoriasis which depend on the JAK-STAT pathway [59, 60].

Tofacitinib is a JAK1 and JAK 3 inhibitor which has been approved by the FDA for the treatment of rheumatoid arthritis. It is being investtigated for the treatment of psoriasis, alopecia areata, atopic dermatitis, and vitiligo, among others [60]. Papp *et al*. showed in two randomized, placebo-controlled studies (OPT Pivotal 1 and OPT Pivotal 2) that oral tofacitinib 5 mg twice daily and 10 mg twice daily is significantly more efficient than placebo after 16 weeks of treatment [61]. Bachelez *et al*. aimed to compare the efficacy of tofacitinib 5 mg twice daily and 10 mg twice daily with that of etanercept 50 mg twice weekly and placebo. At week 12, the authors found a 75% reduction in PASI in 39.5% of patients receiving 5 mg twice daily tofacitinib, 63.6% of those receiving 10 mg twice daily tofacitinib, 58.8% of patients receiving etanercept and 5.6% of patients receiving placebo. The authors concluded that tofacitinib 10 mg twice daily is non-inferior to etanercept [62].

Baricitinib and ruxolitinib are JAK1/2 inhibitors which are currently being investigated for the treatment of psoriasis. Topical tofacitinib and ruxolitinib were also tested in psoriatic patients with some good results but further studies are necessary to support their efficacy [59, 60, 63].

Phosphodiesterase inhibitors

Apremilast

Apremilast is an inhibitor of phosphodiesterase 4 (PDE4), an enzyme which has an important role in degrading cyclic adenosine monophosphate (cAMP) in inflammatory cells. By inhibiting PDA4, apremilast induces elevated levels of cAMP which decreases T-cell secretion of cytokines like TNF-α, INF-γ, IL-17 and IL-23 [58, 64].

Apremilast was approved for the treatment of moderate to severe psoriasis and psoriatic arthritis. It is administered orally, at a dose of 30 mg twice daily [64].

The ESTEEM 1 trial included 844 patients with moderate to severe psoriasis who were randomized to receive apremilast 30 mg administered twice daily or placebo. After 16 weeks of treatment, 33.1% of patients treated with apremilast and 5.3% of those receiving placebo achieved PASI 75 [65].

Some authors propose administering apremilast after the failure of conventional systemic therapy and before biological treatments to reduce treatment costs [66].

Biosimilars

According to the EMA, a biosimilar is a biological medicine highly similar to another already approved biological medicine [67]. Biosimilars are produced after the expiry of the patent of the original product. Biosimilars for infliximab and etanercept are already available for the treatment of moderate to severe psoriasis [68].

Biological therapies have revolutionized the treatment of moderate to severe psoriasis. However, the costs of the treatment are very high and represent a real economic burden for the National Healthcare Systems. Biosimilars are intended to bring the same benefits at a lower price. There was, however, some concern regarding the efficacy and safety of these drugs. Unlike generics, biosimilars have a high molecular weight and a very complex structure. Therefore, even if the amino acid sequence is identical, changes in the tertiary and quaternary structure might affect the efficacy and safety of the drug. On the other hand, different batches of the same reference product are also not identical. Medical agencies have established strict guidelines for the authorization of biosimilars to ensure the safety of those treatments [68-71].

Few studies were done with biosimilars in psoriasis vulgaris but the data available so far supports the safety and efficacy of the products [72-74].

CONCLUSION

Psoriasis is a common disorder with a great impact on the patient's quality of life. Biological therapies have revolutionized the treatment of moderate to severe psoriasis. The data available so far shows that most of these treatments have an acceptable safety profile. Long-term treatment however seems to be associated with a decrease in efficacy. New therapies, which target different molecules involved in the pathogenesis of psoriasis are therefore currently being investigated.

Conflict of Interest disclosure: The authors declare that there are not conflicts of interest.

Psoriazisul este o boală cronică, mediată imun, care afectează aproximativ 2% din populație. Chiar şi în zilele noastre pacienții cu psoriazis se confruntă cu stigmatizarea şi respingerea socială. Drept urmare, calitatea vieții lor este semnificativ deteriorată. Terapiile biologice au revoluționat tratamentul psoriazisului vulgar moderat-sever. Această lucrare îşi propune să treacă în revistă principalele terapii biologice disponibile pentru tratamentul psoriazisului în plăci.

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