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## PSORIASIS AND ITS TREATMENTS: A LITERATURE REVIEW

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**Abstract:** Psoriasis is a dermatological, inflammatory, autoimmune disease with a multifactorial manifestation; however, it is not contagious. The diagnosis involves 2.5% of patients who consulted dermatologists. The research is justified due to reports of low efficacy in controlling the disease, side effects and toxicity, interfering with quality of life. The study aimed to conduct a literature review on psoriasis and its treatments. There are several therapeutic protocols for the treatment of psoriasis, which are chosen according to the severity of the clinical case. Topical therapies are employed in early cases while systemic therapies are used in severe cases. Associated phototherapy reduces treatment time and the adverse effects of topical therapies alone, and yields good results. Among the innovative drugs, immunobiologicals such as adalimumab and secukinumab stand out, which are being used in the prescription of the unified health system and demonstrate the fastest and best results in controlling the pathology.

**Keywords:** therapy, efficacy, safety.

## INTRODUCTION

Psoriasis is a dermatological, inflammatory, autoimmune and multifactorial pathology, however, it is not contagious. The Dermatological Census indicates an incidence of 1,349 diagnoses from a total of 54,519 patients who consulted dermatologists, totaling 2.5%. Characterized by inappropriate T-lymphocyte-mediated immune activation, increased release of pro-inflammatory cytokines, keratinocyte hyperproliferation, and stratum corneum thickening<sup>(1-3)</sup>.

Climate change, emotional stress, consumption of tobacco, alcohol and some drugs, pre-available infectious diseases and obesity are associated with the onset of psoriasis<sup>(4,5)</sup>. The genetic predisposition is decisive, if the parents are carriers there is a

40% propensity to develop it and, when only one of the parents manifests it, the probability reduces to 14%<sup>(5,6)</sup>.

Vulgar or plaque psoriasis is the most common (80%), forming dry erythemoscally plaques, reddish with silvery or whitish scales in regions of trauma, which can reach the entire body<sup>(7)</sup>. Other types include: scalp psoriasis, guttate, inverse or flexural, erythrodermic, palmoplantar or pustular, and psoriatic arthritis<sup>(6,8-10)</sup>. Psoriasis is incurable, so treatment brings relief from symptoms. Therapy is divided into topical medications or phototherapy (associated or not) and systemic medications<sup>(9)</sup>.

Treatment is started topically (tacrolimus, coal tar, anthralin, vitamin D3 analogues, salicylic acid, urea, corticosteroids and retinoids), which affect the proliferation and production of inflammatory mediators. Followed by phototherapy, which involves ultraviolet radiation (UV), associated with psoralen with UVA (PUVA) that causes local immunosuppression, reduction of epidermal hyperproliferation and apoptosis of T lymphocytes<sup>(11-14)</sup>. However, when patients do not respond or are intolerant, systemic drugs are used (methotrexate, acitretin, cyclosporine) or biological agents composed of drugs that integrate anti-tumor necrosis factor alpha (Anti-TNF $\alpha$ ) and include monoclonal antibodies (adalimumab and infliximab), fusion proteins (etanercept) or anti-interleukins 12 and 23 (ustekinumab, anti-IL12 and anti-IL23)<sup>(15)</sup>. Thus, the objective of this research was to carry out a bibliographic survey of updated scientific publications on psoriasis, treatments and therapeutic innovations considering efficacy and safety.

## METHODOLOGY

It involved a systematic, qualitative descriptive research of scientific articles

related to psoriasis and its treatments, published in the last 5 years on the platforms *Scopus*, *Web of Science* and Academic Google, in English or Portuguese and, searched by keywords: “psoriasis”, “diagnosis”, “causes”, “treatment”, “adverse effects”, “innovative”, “efficacy”, “safety” and “toxicity”, in addition to area books. Works that did not contain a clear methodology or efficacy and/or safety of treatments were excluded. The information was organized systematically, promoting discussions on the subject.

## RESULTS

Psoriasis presents lesions in delimited erythematous-scaly plaques, itchy, on trauma surfaces, and can affect the entire skin<sup>(16,17)</sup>. The types of psoriasis and the incidence are shown in Figure 1.

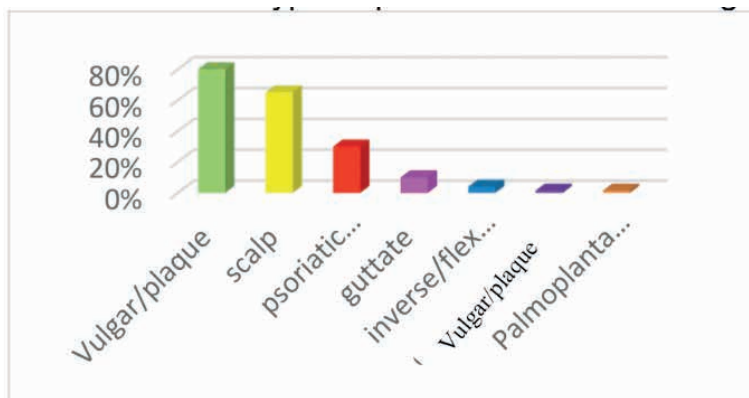
The choice of treatment depends on the degree of severity (9). The first choice is topical treatment, however adherence is sometimes difficult due to reduced patient acceptance and unpleasant application.<sup>(17,18)</sup> Table 1 shows the topical treatments for psoriasis.

Keratolytics eliminate scales, but care must be taken with the continuous use of salicylic acid, due to its nephrotoxic and neurotoxic potential<sup>(10)</sup>. Coal tar has moderate efficacy, increased when associated with UVB. It is not recommended for pustular and erythrodermic psoriasis. Side effects involve folliculitis, eczema and phototoxicity. Therefore, application in sensitive areas such as the face, flexures and genital region is contraindicated<sup>(18)</sup>. Anthralin is a dose-dependent anti-inflammatory, with an effective concentration close to that of the irritant, which makes its use limited due to the appearance of erythema and burning sensation<sup>(10,18)</sup>. Corticosteroids used once a day have moderate to high efficacy, but have side effects with prolonged use: skin atrophy, skin whitening, erythema, dermatitis, acneiform eruptions, infections, cataracts,

and glaucoma<sup>(1,19)</sup>. Vitamin D3 analogues bring visible results after 6 weeks of use, being a safe alternative. Local irritation is the main adverse effect reported, in addition to itching, erythema, burning, folliculitis and pigmentation changes<sup>(18,20)</sup>. Retinoids have mild to moderate efficacy and improvements can be observed in the first two weeks. The retinoid can prevent corticosteroid atrophy, but it is contraindicated in pregnant women, as they cause local irritation. Has increased action when associated with phototherapy<sup>(14)</sup>. Already, tacrolimus is effective for inverse psoriasis compared to plaque psoriasis. The most common adverse effects include mild itching, a feeling of heat at the application site at the start of treatment, which subsides relatively quickly as treatment continues<sup>(21)</sup>.

Natural products are also used topically to control inflammatory processes and reduce adverse effects caused by conventional medications<sup>(17)</sup>. Among them: *Chamaemelum nobile* (Roman Chamomile, oil), *Aloe vera* L (*Aloe vera*, cream 0.5%), *Curcuma Longa* (Curcumin, gel 1%), *Prunus amygdalis var. dulcis* (Sweet almonds, oil)<sup>(24-29)</sup>. Chamomile improved symptoms in psoriasis vulgaris and inflammation, due to the presence of camazulene and mucilage, although no adverse effects have been reported so far<sup>(22)</sup>. The use of *Aloe vera* brings excellent improvement or complete resolution of the lesions. However, it can cause redness, burning and generalized dermatitis in more susceptible individuals<sup>(23,24)</sup>. Heng *et al.*<sup>(25)</sup> evaluated 647 patients with mild to severe psoriasis using curcumin, there was a reduction in plasma concentrations of IL-17, TNF $\alpha$  and INF-g and, it was effective in 16 weeks, with total resolution of 72.2% of patients, without adverse effects<sup>(26,27)</sup>. And, almond oil is also recommended due to its itch-relieving properties<sup>(28)</sup>.

Phototherapy, on the other hand, is used when topical treatments are insufficient or



**Figure 1.** Correlation of the type of psoriasis and its average incidence.

**Source:** Prepared by the author, based on references <sup>(8-10,17,18)</sup>.

Type	Indication for Psoriasis	Terapêutica	References
keratolytics (salicylic acid and urea)	plaques and scalp	3-20% concentration, applied at night	MARTINS; CHAUL, 2009 <sup>(13)</sup> ; SOUSA, 2018 <sup>(10)</sup> .
A coal tar (coalt)	plates	1-5% concentration, 1x/day	CRUZ <i>et al.</i> , 2011 <sup>(19)</sup> ; SOCIEDADE BRASILEIRA DE DERMATOLOGIA, 2012 <sup>(20)</sup> .
Anthralin	common, nail and scalp	Concentration of 0.05-3%, maintaining up to 12 hours of contact with the skin	SOUSA, 2018 <sup>(10)</sup> .
Corticosteroids (clobetasol propionate)	moderate to severe plaques	Concentration of 0.05%, 1x/day	SOCIEDADE BRASILEIRA DE DERMATOLOGIA, 2006 <sup>(21)</sup> ; SUKAROVSKA; LIPOZENČIĆ, 2006 <sup>(22)</sup>
Vitamin D <sub>3</sub> analogues (calcipotriol)	scalp and nails	Concentration of 50 µg/g, 2x/day	SOCIEDADE BRASILEIRA DE DERMATOLOGIA, 2012 <sup>(20)</sup> ; SU; FANG, 2008 <sup>(14)</sup> .
retinoids (tazarotene)	chronic and in plaques	Concentration of 0.05-0.1%, 2x/day	SU; FANG, 2008 <sup>(14)</sup> ; SILVA, 2014
Tacrolimus	mild to moderate plaques	Concentration of 0.03-0.1%, 2x/day	MALECIC; YOUNG, 2016 <sup>(23)</sup>

**Table 1.** Topical medications.

**Source:** Elaborated by the author.

Type	Indication	Therapeutic	References
Narrowband UVB (NB)	guttate and thin plates	Initial dose: 100 mJ/cm <sup>2</sup> , gradually increased to another 40 mJ/cm <sup>2</sup> , 2-3x/week for 3 to 6 months	BRAZILIAN SOCIETY OF DERMATOLOGY, 2012 <sup>(20)</sup> .
PUVA topic	palmoplantar or scalp	Initial UVA dose: 0.12-0.5 J/cm <sup>2</sup> , increasing to 0.12-0.25 J/cm <sup>2</sup> each session, 2-3x/week, up to 30 sessions	CONITEC, 2013 <sup>(34)</sup> ; DUARTE; BUENSE; KOBATA, 2006 <sup>(33)</sup> ; SOUSA, 2018 <sup>(10)</sup> .
systemic PUVA	moderate and severe	Initial dose: 0.5 to 1 J/cm <sup>2</sup> , 2-3x/week for up to 30-40 sessions	BRAZILIAN SOCIETY OF DERMATOLOGY, 2006 <sup>(21)</sup> .

**Table 2.** Phototherapy modalities.

**Source:** Elaborated by the author.

excessively large and scattered lesions occur, indicated for all types of psoriasis because it has anti-inflammatory, immunosuppressive and antiproliferative action, causing minimal or non-existent systemic effect<sup>(20,29)</sup>. The application can be with UVA irradiation (400 – 320 nm, dermis) or UVB (320 – 290 nm, epidermis) and, which can be associated with retinoids, methotrexate, cyclosporine, anthralin and corticosteroids, which lead to rapid control with smaller doses. Table 2 lists the phototherapy modalities, their indication and available therapy<sup>(29)</sup>.

UVB NB radiation is effective from the fifth or sixth session, being safe, with results comparable to systemic PUVA, and can be indicated in pregnancy and for use in children<sup>(20,30)</sup>. Phototherapies are contraindicated for patients with photosensitivity and a history of melanoma or skin cancer<sup>(10)</sup>. However, when these alternatives are not sufficiently effective, systemic therapy is used (Table 3), which is recommended in moderate to severe cases (20-30%)<sup>(1,31)</sup>.

Methotrexate is the most used due to its low cost, excellent efficacy and convenient dosage, but its cumulative liver toxicity prevents prolonged use<sup>(3,32)</sup>. Cyclosporin shows rapid and significant improvement in 80-90% of patients, 50-70% of patients treated with 2.5-5.0 mg/kg/day achieved partial remission (Psoriasis Extension and Severity Index - PASI 75) and 30-50% complete remission (PASI 90) after 12 weeks. Its adverse effects are: nephrotoxicity, systemic arterial hypertension and risk of malignancy<sup>(20)</sup>. Acitretin expresses total remission or an improvement of around 80% of the clinical picture; in 100% in pustular, 83% in erythrodermic and 76.5% in plaque. Adverse effects include dry mouth, eyes and nose, capillary weakness, hypercholesterolemia, are reversible when therapy is discontinued and may eventually

cause cumulative toxicity<sup>(1,2,32)</sup>.

Innovative drugs for moderate or severe cases are used as a second line, although they have a high cost (4-15 thousand reais), which makes their use restricted (Table 4)<sup>(33,34)</sup>.

Infliximab inhibits TNF $\alpha$ , improving symptoms in the first weeks of its use and can be combined with methotrexate. It is well tolerated, however, it can cause dyspnea, urticaria, hypotension, flushing and headache, up to two hours after infusion, and must be controlled in a hospital environment<sup>(35,36)</sup>. Adalimumab binds to TNF $\alpha$ , causing improvement in symptoms of both psoriasis and psoriatic arthritis. In the randomized, double-blind, placebo-controlled REVEAL trial conducted over 52 weeks with 1212 affected patients, 71% achieved PASI 75 compared to 7% on placebo who achieved this PASI at week 16. Its adverse effect is injection site reaction. injection (erythema and/or pruritus, hemorrhage, pain or edema), there is also an increase in infections in the airways and in the genitourinary tract<sup>(33,37)</sup>.

Ustekinumab prevents IL-12 and IL-23 from activating immune cells and is effective for moderate to severe psoriasis. Its side effects include nasopharyngitis, headache, dizziness, upper respiratory tract infection, diarrhea, nausea, vomiting, pruritus, back pain, myalgia, arthralgia, fatigue, erythema and pain at the application site<sup>(38)</sup>. Etanercept inhibits the binding of TNF $\alpha$  and TNF $\beta$  to receptors and its effectiveness has been proven, resulting in a PASI 75 in 49% of cases compared to 3% in the placebo group. There are occurrences of injection site reactions and mild infections<sup>(31,36)</sup>.

Ixekizumab counteracts IL-17A-induced actions and was most effective with biweekly use, being significantly superior to adalimumab and ustekinumab. The most frequent reactions occur at the injection site and upper respiratory tract infections<sup>(39)</sup>.

Systemic agent	Type of psoriasis	Therapeutic	References
<b>Methotrexate</b>	Psoriatic and erythrodermic or pustular arthritis	2.5 mg tablets or 25 mg/mL injection for 2 to 4 months	ARRUDA; MARTINS, 2004 <sup>a(37)</sup> ; BAPTISTA; PILOTO, 2014 <sup>(3)</sup> .
<b>Ciclosporin</b>	moderate to severe vulgaris, pustular and in psoriatic arthritis	2.5 mg/kg/day capsule, divided into two administrations. May gradually increase every 2-4 weeks by 0.5-1 mg/kg/day, up to 5 mg/kg/day for 12 weeks	FAGUNDES, 2007 <sup>(38)</sup> ; SOCIEDADE BRASILEIRA DE DERMATOLOGIA, 2012 <sup>(20)</sup> .
<b>Acitretin</b>	Severe forms of erythrodermic and pustular, localized or generalized	10 and 25 mg capsules for 3 to 6 months	ARRUDA; MARTINS, 2004 <sup>a(37)</sup> ; CONITEC, 2019a <sup>(1)</sup> .

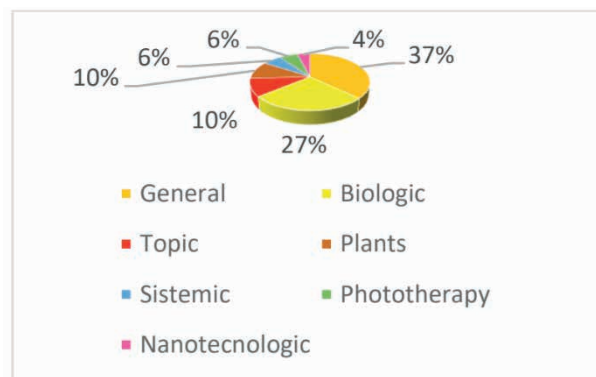
**Table 3.** Approved systemic treatments for psoriasis.

**Source:** Elaborated by the author.

Active principle	Therapeutic	References
<b>infliximab</b>	5 mg/kg IV. Repeat at 2 and 6 weeks.	FERNANDES <i>et al.</i> , 2018 <sup>(41)</sup> ; SOCIEDADE BRASILEIRA DE DERMATOLOGIA, 2012 <sup>(20)</sup>
<b>Adalimumab</b>	80 mg SC. A 40 mg dose follows one week later. Every 14 days, administer 40 mg for up to 16 weeks	AZEVEDO <i>et al.</i> , 2016 <sup>(42)</sup> .
<b>Ustekinumab</b>	45 mg SC at weeks 0 and 4, then repeat every 12 weeks. Stop if there is no response within 28 weeks. Patients with body weight > 100 kg use 90 mg	CONITEC; MINISTÉRIO DA SAÚDE, 2018b <sup>(43)</sup> ; MARQUES; GABRIELA; FELIPE, 2012 <sup>(44)</sup> .
<b>Etanercept</b>	25 mg SC twice a week or 50 mg once a week or twice a week for up to 12 weeks, followed by a dose of 25 mg twice a week or 50 mg once a week for up to 24 weeks	MAGALHÃES, 2016 <sup>(2)</sup> ; MARTINS, 2016 <sup>(39)</sup>
<b>Ixekizumab</b>	160 mg SC (two 80 mg injections) in week 1, followed by 80 mg at weeks 2, 4, 6, 8, 10, and 12, then 80 mg every 4 weeks for 16-20 weeks	CONITEC, 2020 <sup>(45)</sup> .
<b>secukinumab</b>	150 mg/mL SC for 16 weeks. The recommended dose is 300 mg at weeks 0, 1, 2, 3 and 4, followed by monthly maintenance	CONITEC; MINISTÉRIO DA SAÚDE, 2019b <sup>(46)</sup>
<b>Risankizumab</b>	150 mg SC (two 75 mg injections) at Week 0, Week 4, and Week 12 starting after the 2nd dose	CONITEC; MINISTERIO DA SAUDE, 2020 <sup>(47)</sup> .
<b>Golimumab</b>	50 mg SC once a month	CONITEC, 2016 <sup>(48)</sup> .

**Table 4.** Innovative medicines.

**Source:** Elaborated by the author.



**Figure 2.** Distribution of types of treatment for psoriasis.

\* ``General`` refers to articles that address different types of treatments.

**Source:** Elaborated by the author.



Secukinumab neutralizes IL-17A activity and, in the randomized clinical trial CLEAR, demonstrated high efficacy with resolution of lesions (PASI  $\geq$  90). Showed as side effects upper respiratory tract infections, nasopharyngitis, arthralgias, erythema at the injection site, headaches, neutropenia, diarrhea and pruritus<sup>(40,41)</sup>.

Risankizumab inhibits the IL-23 receptor and has been shown to be safe and effective in moderate to severe chronic plaque psoriasis, psoriatic arthritis and Crohn's disease. Upper respiratory tract infections were very common reactions, in addition to superficial mycoses and headaches<sup>(42,43)</sup>. Golimumab, on the other hand, binds with high affinity and specificity to the soluble and transmembrane forms of TNF $\alpha$ , preventing it from binding to its receptor and exerting biological activity. It has the advantage of being applied only once a month. Reactions were upper respiratory tract infections, increased serum levels of liver transaminases, and injection site reactions. Serious effects included one case of prostate cancer and two cases of basal cell carcinoma<sup>(44,45)</sup>.

There are also innovative nanotechnological drugs with polymeric nanocapsules of clobetasol propionate and nanostructured systems containing methotrexate with promising results<sup>(46,50)</sup>. In this study, 50 articles were considered, which addressed treatments for psoriasis, whose distribution is shown in Figure 2.

Although psoriasis has no cure, treatments relieve symptoms and improve quality of life, being selected according to the clinical case. First-choice treatments involve topical ones, however, there is no evidence of a preferred topical medication whose treatment is fast, effective and safe.

## DISCUSSIONS

Topical corticosteroids are well tolerated and

effective and are often replaced by vitamin D<sub>3</sub> analogues or retinoids. Aloe vera stands out as a natural product for presenting the complete resolution of lesions<sup>(18,23)</sup>. Phototherapy has beneficial effects, although it still needs to be better evaluated in terms of long-term safety studies. When associated with medication, it is more effective, reducing treatment time and exposure to ultraviolet radiation, causing relief of symptoms for a prolonged period and reducing side effects. The association of UVB with topical corticosteroids in very resistant psoriatic lesions causes faster regression (maximum regression of 10 sessions in 3 months)<sup>(18,47)</sup>.

Considering systemic therapy, methotrexate, acitretin and cyclosporine demonstrated long-term efficacy; however, they presented a risk of cumulative liver toxicity, which prevents continued use (32,48). Innovative drugs have increased the therapeutic range for severe psoriasis, obtaining efficacy and safety, with a remission profile superior to the other mentioned treatments, in up to 28 weeks. Nanocarrier systems are beginners, requiring further research. Biological drugs have been increasingly indicated and used due to their high efficacy and reduced disease progression<sup>(16,35)</sup>.

## CONCLUSION

There are many pharmacological options available, with topical treatments being the first choice, followed by systemic treatments, according to the severity of the case. These treatments alleviate the symptoms, there is no cure. Therefore, there is a need for research on new drugs with mechanisms of action capable of modulating the immune system and controlling the progression or causing remission of the disease. Closer to this reality, there are immunobiologicals that act as TNF $\alpha$ , TNF $\beta$ , IL-17A and IL-12/23 inhibitors. Of these, Adalimumab stands

out after the CONITEC recommendation (2018) as the first line of treatment after the failure of standard therapy and secukinumab as a second line of treatment in moderate to severe psoriasis, including these drugs are

being used within the scope of the SUS. It was considered that adalimumab offered a lower cost-response and secukinumab had a better clinical response and can be used in adalimumab failure <sup>(49)</sup>.

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