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Brazilian Pharmacotherapy Approaches for Psoriasis Control Using Immunobiological Drugs

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ABSTRACT

Psoriasis is an inflammatory disease of progressive and recurrent autoimmune etiopathogenesis. Its features are skin lesions of varying sizes, with dry scales, silver or gray may appear on any surface of the body, especially in areas of greatest stress or skin resurfacing. Conventional treatments are phototherapy, topical drugs and systemic use. However such treatments are long and can cause toxic effects, thus impairing their long-term use or associated with another treatment. A better understanding of the pathophysiology of psoriasis enabled the development of targeted treatments for specific targets in psoriatic plaque from immunobiological. However, despite these new drugs showed a satisfactory response in the treatment of pathophysiology, are still unknown adverse effects. Help evaluate the effectiveness increases in rates of treatment and identify adverse effects is pharmacist's role in the preparation, monitoring and dispensation of pharmacotherapy for psoriasis. The immune process of psoriasis is associated with many skin alterations. Among them, they can cite the high INFγ levels that deviate dendritic cells IL-12 production in IL-23 that are responsible for maintaining the lesion. Another possibility is the action of Th17 lymphocytes that produce TNF-α and IL-17, associated with the Th22 lymphocytes produce IL-22 inhibits the differentiation of keratinocytes. There is no differentiation occurs hyperproliferation of keratinocytes causing a disorderly release of cytokines. Thus immunobiological drugs are targeted to TNF-α and interleukins (IL-17, IL-22 and IL-23) reduced the immune response to psoriatic plaque, controlling the hyperproliferation of keratinocytes. Another advantage is the low toxicity due to the drug that allows the association to other treatments. The combination of biopharmaceuticals with traditional therapies can provide optimal therapeutic alternatives, being a specific method, non-toxic and economically viable.

Keywords: Psoriasis, Biopharmaceuticals, Psoriatic plaque, Pharmacotherapy for psoriasis

INTRODUCTION

Psoriasis and leprosy were classified together until the late eighteenth century. In the early nineteenth century, Robert Willian carefully and accurately characterized psoriasis and its clinical diseases and Hebra in 1840 definitively separated psoriasis from leprosy. From several epidemiological, immunological and genetic clinical studies carried out mainly in the last 60 years, there is a great evolution of the understanding of the disease [1].

Psoriasis until the 1990s concentrated only on abnormalities in keratinocyte proliferation, believing that this change would be responsible for the disease. Thus, the first treatments of the pathology were topical drugs based on corticosteroids by methotrexate that inhibit keratinocyte hyperproliferation [2].

A major breakthrough in the pharmacotherapy of psoriasis was after evaluating transplanted patients with psoriasis who were receiving cyclosporine that is an inhibitor of the immune system and cytokines that activate the T-lymphocyte. Evident, characterizing an autoimmune disease [3].

Psoriasis is an inflammatory disease of progressive and recurrent autoimmune etiopathogenesis that still has a poorly understood pathophysiology. However, psoriasis is considered to be a dysfunction of immune system cells and cytokine network, i.e., clinical lesions are the result of altered normal epidermal cell growth cycle with concomitant cellular hyperproliferation with inflammatory processes, in which stands out the dense infiltrate of polymorphonuclear

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leukocytes, with characteristic epidermotropism [4].

The spread of psoriatic plaques is rash in areas of constant stress on the skin, such as elbows, knees, pre-tibial region, sacral region, nails and scalp. Because psoriasis is not accurately diagnosed, it can be confused with dandruff, but in joints it can simulate arthritis. Psoriasis can affect the entire skin in 50 to 80% of cases. Patients with severe psoriasis may be associated with more severe comorbidities such as metabolic syndromes, cardiovascular disease, inflammatory bowel diseases such as Chron's disease, depression, panic syndrome, and the consumption of substances such as alcohol and tobacco follow up with a multidisciplinary team [2].

It is also known that it is a non-communicable skin disease, occurring more frequently between 15 and 30 years, in both sexes, affecting about 1 to 3% of the world population with great impact on patients' quality of life [5].

The most common form of the disease is psoriasis vulgaris, which is characterized by lesions of varying sizes, with dry, silver or gray scales that can appear on any surface of the body, classified into three categories: mild, moderate and severe, which is responsible for 85-90% of cases. If left untreated, psoriasis can develop into psoriatic arthritis, which is the form present in 6 to 40% of patients with pathophysiology, which involves nails, axial skeleton, peripheral joints, sacroiliac and enthesis which if left untreated evolve to injury and permanent joint deformity. The less common forms are reverse psoriasis, pustular, erythrodermic, palmoplantar and guttate [6].

Psoriasis is a disease with great social impact on the patient's life. A study showed that in Portugal more than 250,000 people are affected by this disease, which causes physical and mental discomfort, thus causing psychosocial comorbidities. Psychic impairment leads some patients to alcohol and tobacco consumption, compromising the immune system, accentuating the disease picture with the appearance of more psoriatic plaques [2].

The pathophysiology of psoriasis is related there are psychic changes. Because it is an autoimmune disease, it affects the body as a whole, that is, any change in its psychic state may be associated with high percentages of spread of lesions [7].

Currently, patients with severe and moderate psoriasis treat with topical or corticoid-based drugs and conventional systemic therapies such as methotrexate, acitretin and cyclosporine, which limit their continued use because of their toxicity [8].

In recent years, based on new research on the pathophysiology of psoriasis, new treatments have been developed to target specific psoriatic plaques. The immunobiologicals used in the treatment of psoriasis correspond to antibodies, cytokines (IL-12/IL-23) and fusion proteins, which is a human tumor necrosis factor p75

receptor protein produced by recombinant DNA technology in an expression system. Mammalian these drugs act by modulating the immune response reducing damage caused by autoimmunity [9].

Although these new drugs have a satisfactory response in the treatment of pathophysiology, their adverse effects are still unknown. Helping to evaluate increases in treatment effectiveness indices and identifying adverse effects is the pharmacist's role in the design, follow-up and dispensation of pharmacotherapy for psoriasis.

METHODS

This study is a bibliographic review in which were searched in scientific articles topics on the subject in databases such as Google Scholar, Scielo Brazil, Periodicals Capes and Brazilian Digital Library of Theses and Dissertations.

The study was conducted using publications from any country in the world, without language restriction, obtained in full from 2000 onwards. The descriptors used in the research were: "psoriasis"; "Immunobiological"; "Psoriasis pharmacotherapy" and "psoriasis monoclonal antibodies".

Immune response

Psoriasis is a multifactorial chronic disease that presents an immune-mediated inflammatory response. It is suggested that it is influenced by genetic, environmental (emotional stress, medication, trauma, infections, weather) and behavioral factors. Although its pathophysiology is not yet defined, it is believed that the disease is triggered by inflammatory phenomena mediated by T-lymphocytes [2].

To understand the immune dysfunction of the pathology, it is relevant to understand skin changes, especially the physiology of keratinocytes, relating the action of dendritic cells, macrophages, neutrophils, mast cells, endothelial cells and T lymphocytes [10].

Currently, the pathophysiology of psoriasis is described by an immune process that begins after a series of stimuli related to environmental factors, such as emotional stress and/or medications that can trigger the inflammatory process against keratinocytes.

It is suggested that the initial stimulation for keratinocyte hyperproliferation starts from a dysfunction of the immune system with increased production of proinflammatory cytokines that activate dendritic cells. Dendritic cells present antigen to circulating naive T lymphocytes. Adhesion molecules (ICAM-1) initiate the process of a mediated immune response, leading to the release of interleukins IL-12, IL-23, IL15, cytokines TNFα (tumor necrosis factor-alpha), INFα (interferon-gamma) resulting in targeting of immune system cells to the site of inflammation. T-lymphocyte activation promotes differentiation into Th-1 or Th-17 subtypes with cytokine production and release of mediators involved in the inflammatory pathway IL-12/Th1

(IL-2, INF-γ and TNF-α), IL-23/Th17 (IL-6, TNF-α, IL-17, and IL-22) [6].

The-17 cells stimulate IL-17 production, which in turn induces the production of chemokines that play an important role in the pathophysiology of recruitment of neutrophils, CD8+ T lymphocytes and dendritic cells mediating early tissue inflammation, causing psoriatic injury [2].

The immune process of psoriasis is associated with many epidermal changes. These include interferon-gamma (INFγ),

which in dendritic cells that divert the production of IL-12 to IL-23 that is responsible for the maintenance of the lesion. Another possibility is the action of Th17 lymphocytes that produce TNFα and IL-17, which associated with Th22 lymphocytes produce IL-22 inhibiting keratinocyte differentiation. If there is no differentiation there is a hyperproliferation of keratinocytes causing a disordered release of cytokines, inducing an inflammatory process in the dermis that characterizes the psoriatic plaque **(Figure 1)** [11].
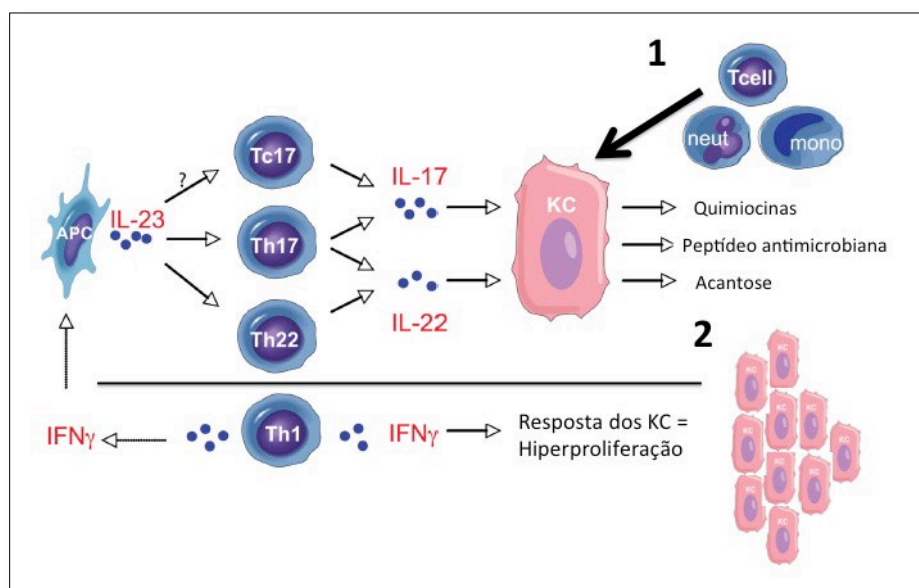

Figure 1. The action of an immune response in the psoriatic lesion. Antigen-presenting cells (APC) release Il-23 which induces activated cytotoxic T lymphocytes (Tc17) and T helper (Th17) to release Il-17, which together with Il-22 released by a T helper lymphocyte subpopulation (Th22), induce keratinocyte (Kc) responses by releasing chemokines and antimicrobial peptide. With the release of chemokines, inflammatory cells (T cell; neutrophil and monocyte) increase their activity. Another response to the action of Il-17 and Il-22 is acanthosis. In parallel, type 1 T helper lymphocytes release interferon-gamma (Infγ), which increases APC activity and enhances acanthosis.
Source: Adapted from Nograles et al. [12]

Pasi

Psoriasis area and severity index (Pasi) is used to assess disease severity and can range from 0 to 72. An index greater than 18 means severe disease. The Pasi 75 reference means a 75% reduction in the pretreatment index and is used to evaluate therapeutic success. Relapse of the disease is considered when there is a 50% increase in this index after a period of improvement. Pasi, however, does not consider the impact of the disease on quality of life, which in daily clinical practice is important when choosing treatment [13].

Conventional therapies

Psoriasis is a chronic inflammatory disease, and the choice of treatment must take into account age, gender, occupation, existing diseases and other health problems. There are several treatment options for pathology, with various mechanisms of action, which may interfere in different parts

of the immune system and others only in the proliferation of keratinocytes. Treatments can be topical use, phototherapies, systemic drugs and immunobiological [14].

Corticosteroids: Topical corticosteroid for mild pathology has rapid and effective effects on disease onset because it is anti-inflammatory, immunosuppressive (reduces activation or efficacy of the immune system) and anti-mitogenic (inhibiting proliferation) action. Despite its therapeutic advantages, its interruption causes a greater appearance of psoriasis rash, usually more severe than the pre-existing one and often presents tachyphylaxis (losing its effect in prolonged use) [4].

Methotrexate: Methotrexate acts by interfering with cell replication (cytotoxic) indicated in the treatment of psoriatic arthritis, psoriasis or erythrodermic forms. Its mechanism of action is through the dihydrofolic acid-reducing enzyme that synthesizes tetrahydrofolate inhibiting the formation of

purines and, consequently, the synthesis of RNA to DNA. Thus having a good result in psoriasis by its action that is DNA replication, as in the case of keratinocytes in psoriasis eruptions, and also having an action to decrease immunological (immunosuppressive) activity [15].

Methotrexate can be given orally and I.V, although it requires strict control because of its adverse effects that require constant laboratory tests, as it has important hepatotoxic potential. Thus it has to make a careful evaluation to each individual [15].

Cyclosporine: Cyclosporine is a major inhibitor of the immune system is mainly used to prevent organ rejection. Cyclosporin acts by inhibiting cytokine production and release, including IL-2 and also by inhibiting cytokine release by activated T cells. Cyclosporine should not be given in pregnancy and its nephrotoxicity can trigger high blood pressure and heart problems. Because of its immunosuppressive action, there is a higher risk of infections and the development of malignancies. It also requires frequent examinations, careful evaluation and monitoring because of its hepatotoxic potential [4].

Acitretin: Acitretin is a second-generation drug used to treat patients with cutaneous T-cell lymphoma and belongs to the class of vitamin A-derived retinoids. As a synthetic aromatic retinoic acid analog, its function would be to bind to nuclear receptors by altering expression. Of a series of genes, but its mechanism of action is still undefined in psoriasis, which leads to the belief that it has an immunomodulatory and anti-inflammatory effect, acting on the growth and differentiation of epidermal cells [15].

In the epidermis, retinoids may induce expression of differentiation markers and exhibit inhibitory effects on keratinocyte proliferation. It is used in cases of generalized plaque psoriasis. In resistant cases may be associated with phototherapy. The most common side effects are photosensitivity, paronychia, chelitis, xerosis, pure, epistaxis, conjunctivitis, periungual granulomas and alopecia. The adverse effect of the medication is restricted to its use in women of childbearing age due to teratogenicity. The medication is available in 10 and 25 mg capsules and the recommended dose is 0.5 to 1.0 mg/kg/day **(Table 1)** [15].

Table 1. Conventional pharmacotherapy for psoriasis control provided by the Brazilian Health System.

Drug/dose	Efficiency	Side effects	Contraindications
Methotrexate 7.5 or 25 mg VO or IM OR SC Children: 0.2-0.4 mg/kg	PASI 75 at week 16 36% to 60% Does not usually induce complete remission	Teratogenicity, hepatoxicity, pulmonary fibrosis embryopathy, nephrotoxicity	Pregnancy, lactation, liver cirrhosis, active liver infection, hepatic and renal insufficiency, obesity and the elderly
Acitretin 0.5 to 1.0 mg/day always after meal VO Children: 0.4-0.5 mg/kg/day	Mild to moderate high if associated to phototherapy.	Fetal abnormalities or death, skin mucus toxicity, increased liver enzymes, hyperlipidemia	Pregnancy up to 3 years of drug withdrawal liver disease, alcoholism, osteoporosis, hyperlipidemia
Cyclosporine 2.5-5.0 mg/kg/day ORAL DOSE	PASI75 at 70%	Renal impairment, hypertension, immunosuppression, hypertrichosis, gingival hyperplasia, lymphoma	Kidney changes, uncontrolled hypertension, history of malignancy Controlled hypertension, immunodeficiency, active infection, attenuated virus vaccination, alcoholism, liver disease

PASI 75: Means a 75% reduction in the pre-treatment rate and is used to assess therapeutic success
Source: *Adapted from Brazilian Ministry of Health [16]*

Non-pharmacological associated treatment – Phototherapy

Phototherapy is used to treat various dermatoses with UVA and UVB irradiation. In psoriasis, phototherapy can be used with other drugs to decrease treatment and doses used by drugs such as corticosteroids, methotrexate and acitretin. Phototherapy is used for its anti-proliferative, anti-inflammatory and immunosuppressive activity. This treatment leads to a decrease in cells on the antigen-presenting surface and consequently decreases the activation of T lymphocytes. Phototherapy can be used alone or in combination with other topical and/or systemic medications, thus seeking to decrease the doses of both drugs radiation, reducing both side effects and maintaining therapy. Side effects include nausea, headache, dizziness, herpes simplex, etc. Symptoms in which patients should be aware that there may be a slight increase in photoaging, cataract and risk of skin cancer among other symptoms [17].

Conventional systemic medicines have a satisfactory response to the treatment of moderate to severe psoriasis but cause numerous adverse effects such as hepatoxicity and teratogenicity. Also, treatment is discontinued due to dose and/or period.

With a better understanding of the pathophysiology of the disease, it was possible to develop new drugs. Through immunobiological drugs that act specifically to mitigate immunopathogenic changes. Immunobiologicals are developed through the use of recombinant biotechnology and are called biological agents that have revolutionized the treatment of moderate to severe psoriasis. However, in addition to the observed efficacy, one of the great advantages over existing drugs is the safety profile with no toxicity in target organs [6].

In this reality emerged the immunobiological agents. Currently, in BRAZIL, there are four ANVISA approved biological drugs for the treatment of psoriasis: Adalimumab, Infliximab, Etanerceptte and Ustekinumab, which are used in cases of moderate to severe psoriasis [13].

These new classes of treatments consist of recombinant molecules developed from living organism gene sequences. They are fusion proteins and monoclonal antibodies that specifically target the activity of inflammatory T cells or cytokines by inhibiting or modulating specific immune system agents. Biological drugs can save other organs and minimize side effects. However, biological therapy has been associated with lower toxicity than previously used systemic treatments [2].

Among the biological therapy tools, monoclonal antibodies (mAb - Monoclonal Antibodies) stand out, giving rise to the sulphix MAB (MABE) in drug nomenclature. The mAb's production method generates different definitions:

Human Monoclonal Antibodies are genetically engineered and have the characteristic of not being immunogenic since the amino acid sequence in their content is identical to that of human antibodies.

Humanized Monoclonal Antibodies are murine monoclonal antibodies that are fused to humanized antibodies to acquire Fc portion of the human antibody and are substituted on the Fab portion by specific amino acid sequences aimed at decreasing their immunogenicity.

Chimeric Monoclonal Antibodies are hybrid immunoglobulins using the constant region from a human antibody and the variable region from a mouse antibody.

Another biological molecule used for pharmacological action is fusion proteins, which by definition are cell surface receptors bound by the constant portion (Fc) of a monoclonal antibody (fused proteins), which seek to mimic components responsible for cellular signaling in the inflammatory cascade [18].

Regarding the safety of treatment with biological agents, patients have to go through a thorough and adequate laboratory investigation to ascertain their history. Immunobiologicals are known to facilitate the onset of opportunistic infections and reactivation of latent infections and may also alter the course of occult neoplasia. Thus offering a necessary safety in the administration of these immunosuppressive drugs to patients [13].

Regarding the immunobiological drug due to its high cost and limited availability in the Unified Health System (SUS), only a few patients receive direct release and many patients need to resort to legal means to receive treatment which can often delay the treatment [13].

TNF-α inhibitors

Tumor necrosis factor (TNF-α) is a naturally occurring cytokine, compromised in normal immune system inflammatory responses [4].

TNF-α inhibitors bind to the TNF-α cytokine produced by macrophages, monocytes, neutrophils, T cells, CAA and keratinocytes preventing their binding to the receptor and hence its proinflammatory action. The most common adverse effect during the administration of these drugs is injection site reactions such as erythema, pruritus, pain, edema and in rare cases anaphylactic shock. These drugs should be used with extreme caution in patients with heart failure due to several reports indicating the occurrence or worsening of congestive heart failure in patients using this medication [19].

Etanercept (Enbrel®): Etanercept is a TNF-α receptor fusion protein linked to the human immunoglobulin (IgG1) p75 Fc fraction. The drug is a competitive inhibitor of TNF-α which prevents interaction between this cytosine and its cell surface receptors. Etanercept also modulates the activity

of other inflammatory cytokines and does not induce complement-mediated cell lysis *in vitro* [20].

Adalimumab (Humira®): Adalimumab is a recombinant humanized monoclonal antibody that specifically binds TNF for its high affinity and high specificity, nullifying its biological function by blocking its communication with cell surface TNF (p55 and p75) surface receptors [4].

In existing studies with Adalimumab, it was reported that 70% to 80% of patients with the condition had improvement at 16 weeks, showing a big difference from methotrexate which achieved only 35% improvement in the same period [4].

Infliximab (Remicade®): Infliximab is a murine human IgGI chimeric monoclonal antibody obtained by artificial DNA sequence technology that results from the combination of different DNA sequences. This drug binds with high affinity to soluble and transmembrane forms of TNF. Thus with a high affinity, forming a stable cluster that prevents the

binding of tumor necrosis factor-alpha, thereby decreasing the expression of proinflammatory cytokines [21].

Interleukin inhibitors

Interleukins IL-12 and IL-23 are produced by activated dendritic cells. Interleukins IL-12 stimulates the differentiation of naive T cells into Th1, which produce TNF, INF and IL-2. Interleukins IL-23 promotes activation and differentiation of Th-17 cells, which secrete interleukins IL-17, IL12 and TNF, protagonist interleukins in the pathogenesis of psoriasis [18].

Ustekinumab (Stelara®): Ustekinumab is a monoclonal antibody that acts against IL-12 and IL 23 p40 subunits, cytokines related to the transformation of naive T cells into Th1 and Th17 cells. The role of the IL-12 and IL-2 mediated pathway in the mechanism of various inflammatory diseases, especially psoriasis, has been well recognized **(Figure 2 and Table 2)** [18].
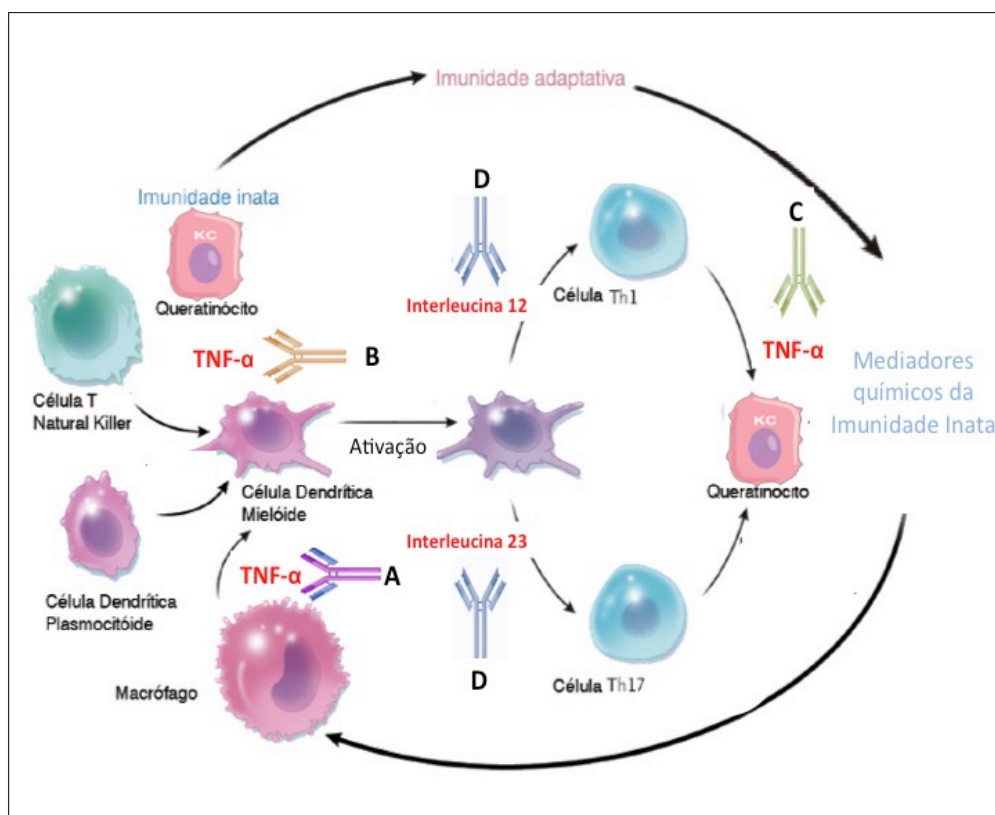

Figure 2. The target of the action of immunobiological drugs on the immune response of psoriasis. Immunobiological drugs act on TNF-α inhibiting its action on immune cells and keratinocytes. The difference between monoclonal antibodies is the action stage on TNF-α. A - Entercept, is an IgG1 that recognizes the p75 fraction of TNF-α, preventing the action between macrophage and dendritic cell; Adalimumab is a humanized immunoglobulin recognizing TNF-α p55 p75 fractions, preventing the innate response of the natural killer lymphocyte; C - Infliximab is an IgG1 that recognizes the soluble form and transmembrane portion of TNF-α; D-Ustekinumab is an IgG1 that recognizes IL-12 and IL-23, p40 fraction inhibiting Th1 and Th17 lymphocyte responses, respectively, on keratinocytes. By inhibiting the effect of TNF-α on keratinocytes, psoriatic plaque formation can be contained.
Source: *Adapted from Diamantine; Ferreira [6]*

Table 2. Pharmacotherapy with immunobiological to control psoriasis provided by Brazilian Health System.

Drug/Dose	Epitope/binding site	Effectiveness	Contraindications/Side effects
ETANERCEPTE Fusion protein. 25 mg SC twice a week or 50 mg SC twice weekly monotherapy	(anti-TNF-α)	At a dose of 25mg 2x per week PASI 75 with 12 weeks of treatment 34% PASI 75 (with 24 weeks of treatment) 44% At 50mg dose 2x per week PASI 75 at 12 weeks 49% PASI 50 with 12 weeks 74% 24 without 77%	Tuberculosis Infections Local reactions where the injection is applied Aggravation of Congestive Heart Failure
INFLIXIMABE Chimeric monoclonal antibody 5 mg/kg by infusion	(anti-TNF-α)	PASI 75 with 10 weeks of treatment 80.4%	Infusional Reactions Acute or delayed Infections, malignancy or lymphoproliferative disease, aggravation of congestive heart failure
ADALIMUMABE Monoclonal Antibody 80 mg via SC in the first week. 40 mg via SC every 15 days. 40 mg weekly	(anti-TNF-α)	PASI 75 with 24 weeks; without 49%. PASI 50 with 24 weeks without 75%	Tuberculosis Malignancy, hemolymphoproliferative diseases active or chronic infections
USTEKINUMAB Via SC 45 mg administered at weeks 0 and 4 and, then every 12 weeks. In patients with bodyweight greater than 100 kg, 90 mg dose may be used.	Recombinant Antibody anti-IL-12 e IL-23	PASI 75 16 weeks 80% adalimumab 36% MTX 19% placebo PASI 75 at 12 weeks: 27% PASI 75 at 24 weeks: 44%	Tuberculosis Malignancy

PASI 75: Means a 75% reduction in the pre-treatment rate and is used to assess therapeutic success
Source: *Brazilian Ministry of Health, 2012 [16]*

Immunobiologicals represent a new modality of therapy for psoriasis. But due to the chronicity of the disease and the high cost of immunobiological and their unknown adverse effects, associations with conventional drugs such as

methotrexate, acitretin, cyclosporine, and phototherapy are suggested. In this condition, the effects of each drug are potentiated and may use lower doses and consequently with less toxic effects. Another advantage in the association of immunobiological with traditional drugs is the reduction in the cost of treatment **(Table 3)** [22].

Table 3. Suggested conventional pharmacotherapeutic associated with immunobiological.

Traditional Drugs	Immunobiological Drugs	Synergistic Effects
Methotrexate	Etanercept Infliximab Adalimumab	(MTX) Cell proliferation (anti-TNF-α) (anti-TNF-α) (anti-TNF-α)
Acitretin	Etanercepte Inflixamabe Adalimumab	Epidermal cell growth and differentiation (anti-TNF-α)
Cyclosporine	Etanercepte Adalimumab	Immunosuppressive (anti-TNF-α) (anti-TNF-α)

Source: Brazilian Ministry of Health, 2012 [16]

CONSIDERATIONS

Pharmacotherapy with immunobiological has advantages over the treatment of systemic drugs (traditional treatment), due to the specificity and the absence of pharmacological toxicity. Combining immunobiological with traditional therapies can provide optimized therapeutic alternatives for patients who respond inappropriately to a single pharmacy strategy. Additionally, therapeutic efficacy may be increased by supplementation with another associated systemic drug [23].

Traditional therapies for psoriasis are often unable to meet desired treatment goals, mainly due to high doses and long-term use causing toxicity. Combination pharmacotherapy offers psoriatic patients a specific method with low pharmacological and toxicological risks [24].

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