Guselkumab as a Possible New Treatment for Psoriasis

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ABSTRACT

Introduction: In Mexico it affects approximately 2 million people, with a significant impact on quality of life and difficult to manage.

Theoretical framework: The lesion it causes is round, salmon-pink papules and plaques, located on knees, elbows and scalp. The diagnosis is mainly clinical and the treatment will depend on the affected body surface and the location. The drugs considered first line are topical and second line drugs are used systemically, which in many occasions have adverse effects that make attachment difficult.

Discussion: Guselkumab, a drug approved in 2017, is an IgG1 that blocks the p19 subunit of IL-23.

Conclusion: Researching new drugs helps us to provide the patient with a treatment with the least amount of adverse effects, achieving greater adherence and better control of the disease.

INTRODUCTION

Psoriasis affects 125 million people; it is estimated that in Mexico it has a prevalence of 2 million inhabitants (1). It has a significant impact on the quality of life of people who suffer from it, both physically and emotionally with the consequent affection in the interpersonal relationships of individuals and the affection of multiple organs, which causes the appearance of various complications such as psoriatic arthritis, cardiovascular disease, diabetes, non-Hodgkin's lymphoma, cutaneous T-cell lymphoma and increases the risk of psychiatric diseases such as depression and anxiety. (2) (3)

Hence the importance of providing treatment that improves the patient's symptomaticity and thus his or her quality of life.

The term psoriasis derives from the Greek "psora", which means itching (2). Throughout history, hypotheses have been created about the etiopathogenesis of the disease, including inadequate hygiene, microbes, allergies, among others (3).

The development of these hypotheses has led to changes in the treatment of the pathology. Hippocrates was the first physician to use coal tar to increase sensitivity to sunlight, Galen recommended the use of arsenic (3). In the 1800's the use of tar, arsenic and sunlight continued as a treatment for psoriasis, it was until 1960 when psoriasis was considered of autoimmune origin, therefore the treatment was updated, the effect of sunlight was replaced by the administration of ultraviolet radiation in the affected areas of the skin and biological drugs were introduced to the market at the end of the 20th century, thanks to the human genome project, in which the genes associated with the disease were determined (3).

For the aforementioned reasons, this research was carried out in order to identify the disease in a timely manner, in addition to establishing an adequate management by comparing current therapeutics with drugs that are beginning to be used in the treatment of the disease, since despite the effect caused
in the quality of life of patients, it is frequent that an effective diagnosis and treatment is not carried out, mainly due to poor adherence caused by side effects, in addition to the fact that often the complications of the disease are not detected in time, so the long-term results are less favorable (3). Many patients suffering from the disease seek initial evaluation at the primary care level, therefore it is important that physicians are well informed of the different therapeutic options to achieve the greatest benefit with the least number of side effects, based on the characteristics of the patient and the drugs used, therefore not only included the diagnosis and management of psoriasis, this research also covers the etiological, pathophysiological, histological, epidemiological aspects and the manifestations that occur in the pathology (4).

THEORETICAL FRAMEWORK
Definition
Psoriasis is an inflammatory dermatosis, it is chronic and is mediated by the immune system, that is to say, it has an autoimmune origin. It is a cause of erythema and desquamation all over the body called "erythroderma". It occurs most frequently on the skin of the elbows, knees, scalp, lumbosacral areas, intergluteal folds and, in the case of men, the glans penis.(5)

Epidemiology
Psoriasis is one of the most frequent dermatological diseases (6,7). In Mexico, the incidence is 2% of the total population, of which 77% suffer from mild psoriasis and the rest from moderate to severe psoriasis. The arthropathic form of this disease represents a percentage of 1 to 15%. It predominates in young adults, between 20 and 40 years of age, although 33% have its age of presentation before the age of 20 years (1). Psoriasis is sometimes associated with myopathy, enteropathy, cardiovascular disease and AIDS, where the frequency varies from 1.3 to 2.5% (6,7).

Etiology
It is idiopathic, although it has been linked to a cause(1):
- Genetics.
- Increased proliferation of epidermal keratinocytes and alteration in their differentiation.
- Immune.
- Neurogenic.
Obesity, smoking and alcoholism are factors that exacerbate the severity of psoriasis (8).

Pathology
The causative antigens are not yet well understood, however, it has been linked to sensitized populations of CD4 Th1 and Th17 lymphocytes and cytotoxic CD8 T lymphocytes, known to enter the skin and accumulate in the epidermis.
- These cells are responsible for stimulating the proliferation of IL-12, IFN-γ, TNF-alpha and IL-17, responsible for the symptomatology of the patients causing a favorable response in the treatments in charge of blocking TNF; although growth factors are also stimulated producing a proliferation of the keratinocyte and in this way will give rise to the typical lesion of psoriasis. Histologically, the stratum granulosum will be thinned or absent and an extensive hyperkeratotic scale is observed. The proliferation of epidermal cells that occurs in the disease generates acanthosis. (5)

CLINICAL MANIFESTATIONS
The lesion is characterized by round, salmon-pink, well-defined papules and plaques, covered by a silvery micaceous desquamation, with variable pruritus (No 1, 6). There are 4 types of presentation (6):
- Psoriatic plaque (present in 90% of patients) (9) is a stable, slow-growing plaque, generally symmetrical, affecting elbows, knees, intergluteal folds and scalp.
- Inverse Psoriasis: Located in the armpits, groin, submammary region, navel, scalp, soles of hands and feet.
- Eruptive psoriasis (guttate psoriasis): frequent in children and young people. There are multiple small erythematous and scaly papules. There may be a previous history of a respiratory infection secondary to beta-hemolytic streptococcus.
- Pustular psoriasis: erythematous lesions, with pustules and scales that are located on soles and palms or may be generalized.

Thirty percent of patients with psoriasis have psoriatic arthritis (6); they can be symmetric, asymmetric, distal interphalangeal, spondylitis, and mutilating arthritis. The prevalence of nail psoriasis is between 50 to 80% (9), this incidence increases when it is of the psoriatic arthritis type to 70% (10). It consists of a change in color to yellow-brown, with dimpling, depressions, separation of the nail plate from the underlying bed, thickening and crumbling. Rarely occurring as the only manifestation, it can cause significant pain and discomfort, affecting the quality of life of individuals. (10)

Psoriasis can lead to social isolation, anxiety, distress and decreased self-esteem (8).

DIAGNOSIS
The diagnosis of this disease is mainly clinical (11). Skin lesions should be examined and changes in nails and joints that are compatible with psoriasis should be intentionally sought (11). The Auspitz sign, Duncan's membrane sign or Koebner's phenomenon can be looked for to help establish the diagnosis (11). In atypical clinical presentations these signs and the search for extracutaneous manifestations can help to make the diagnosis. Finally, if the definitive diagnosis has not been established, a needle biopsy can be performed in which we would find the histopathological alterations typical of the disease (11). Such as hyperkeratosis with parakeratosis, acanthosis and lack of the granular layer, formation of
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Munro-Sabouraud microabscesses in the stratum corneum (1).

If any laboratory and laboratory tests are altered, it is usually due to manifestations of accompanying diseases that are common in these patients, such as metabolic syndrome, renal failure and autoimmune diseases such as rheumatoid arthritis, SLE, autoimmune thyroiditis and vitiligo (1).

In patients with psoriasis, the presence of proinflammatory cytokines can be found in blood and in psoriatic lesions. Four cytokines are able to predict the disease with a sensitivity and specificity of 100%, these are IL-17, 12, 22 and adiponectin (12).

TREATMENT

For the treatment of psoriasis it is important to cover all the areas it affects. Starting with the psychological impact it has on patients. Therefore, a broad explanation and supportive psychotherapy are recommended (1).

The pharmacological treatment will depend on the extension and location of the psoriasis, and this is susceptible to change with time, generate tolerance or toxicity. Social factors, the patient’s lifestyle, cultural level and adherence to treatment as well as economic factors and availability of therapies should not be left aside, (13) since it is estimated that therapeutic compliance is only good in 33.3% and regular in 66.7% (7).

Starting with topical treatment, which is the first choice (13), there is a wide variety of drugs that can be used, all of which can be used in the case of mild to moderate psoriasis. In the Mexican CPG, the treatments that are considered first-line are topical corticosteroids, vitamin D3 analogs and retinoids (tazarotene). Both vitamin D and tazarotene are safe therapies in which good responses have been seen, and have replaced the use of tar, salicylic acid and anthralin, (6) which tend to present more side effects. With topical corticosteroids it is important to review the extension and topography of the lesion and the age of the patient to choose the potency. (7)

Low potency corticosteroids are used on the face, intertriginous areas, thin skin, in children, and for short periods. For chronic thick plaques, high potency can be used, without extending the use beyond 4 weeks. (13) It is important to remember that tachyphylaxis may occur with long term use, and they cause a suppressive effect on the adrenal glands. (7)

In second line, a calcineurin inhibitor is recommended as an alternative in facial and inverse psoriasis, which have been refractory to first line treatment; its most frequent effects are headache, nausea, vomiting, hypertension and renal alterations. (6,11)

The third line includes coal tar, salicylic acid and urea, which, as mentioned above, have adverse effects that are bothersome for patients (7).

The recommended second choice treatment is systemic. Administered orally. It is mainly used in moderate to severe psoriasis or if first-line treatment in moderate to mild forms fails. Its limitations are due to the side effects that occur in the long term, so it is necessary to periodically review if there is an impact on the patient. Cyclosporine, methotrexate, retinoids (acitretin), and to a lesser extent azithromycin have been studied. The latter has a myelosuppressive effect, so it is the least used, however evidence has emerged that it can be combined with biologics to replace cyclosporine, it is recommended to evaluate thiopurine methyltransferase levels as a parameter to determine the starting dose. Cyclosporine therapy can be used for up to 2 years, it is important to adjust doses, reducing them to reduce adverse effects such as neurotoxicity and secondary hypertension; it is recommended to evaluate creatinine levels monthly and glomerular filtration every year. Before initiating the use of methotrexate it is necessary to perform laboratory tests such as BH, PFH, hepatic US, and pregnancy test, since it has absolute contraindications in pregnant or breastfeeding women, cirrhosis, alcoholism, and its use with folic acid is recommended for greater safety. Acitretin in moderate to severe psoriasis is not recommended because higher doses, with more side effects, are needed to obtain the desired effects. (7,13)

With new studies indicating that psoriasis is a T-lymphocyte-mediated disease, as mentioned in pathogenesis, targets for new treatments were sought, from which the biologics emerged, which include: Adalimumab, Etanercept, Infliximab and Ustekinumab. All of these are TNF alpha inhibitors, applied subcutaneously, with the exception of Infliximab, which is intravenous. These substances are usually well tolerated and are quite effective, reducing the changes in work responsibility due to the disease and the time of illness (7); however, most of them have adverse effects that can aggravate or cause other disease, serious infections, hepatotoxic effects, congestive heart failure, hematological episodes, hypersensitivity reactions, neurological episodes, possibility of more cancers (6); however, some studies (14) have shown that they did not generate an increase in the risk of malignancy.

For example, Adalimumab is contraindicated in pregnant women and in patients with congestive heart failure. Alefacept can reduce CD4 levels, so it is important to count CD4s before and during treatment and discontinue if the count is below 250 cells/ml.

Most are useful for moderate to severe psoriasis when other treatments have not responded, however, they are expensive. Infliximab is a very good option for the treatment of psoriatic arthritis (11).
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Even when psoriasis and psoriatic arthritis are controlled, nail involvement may persist, due to poor penetration of topical medications, pain associated with injections into the lesion, and adverse effects. Recommendations for patients with disease limited to the nails, high potency topical corticosteroids with/without calcipotriol may be used. In those who fail topical therapy, Adalimumab, Etanercept, intralesional corticosteroids, Ustekinumab, Methotrexate and Acitretin are recommended. In those with skin, nail and even joint involvement, Adalimumab, Etanercept and Ustekinumab are widely recommended. (10)

A study compared the efficacy of two drugs used to treat the disease; Ustekinumab inhibits the p40 subunit of IL-23, making it effective in the treatment of psoriasis; and Risankizumab, which rapidly and sustainably reduces skin lesions, is an IgG1 monoclonal antibody that selectively inhibits the p19 subunit of interleukin 23. The study showed that Risankizumab at a dose of 90-180 mg starts to act faster and has a more prolonged effect than the other drug, and that it also improves the symptoms of psoriatic arthritis (14).

Phototherapy is another option, especially when psoriasis is extensive, i.e., when more than 20% of the body surface is affected. (1) In clinical practice, ultraviolet B light (UVB), narrowband UVB and ultraviolet A light (UVA) with topical and oral psoralens (PUVA) are used; due to their immunosuppressive properties, they tend to cause mutations that increase the incidence of melanoma. It is contraindicated in patients using cyclosporine, and is not recommended in immunosuppressed patients. (6, 13)

Despite the variety of therapies used in psoriasis, 52.3% of patients report dissatisfaction with their treatment due to ineffectiveness or adverse effects, and 51% report the use of alternative and complementary medicine. (15)

Foods with systemic anti-inflammatory effects are more likely to improve symptoms. These include monounsaturated fatty acids (MUFA), fish, vitamins A, C, D, and E, and omega-3 fatty acids. MUFA and anti-inflammatory nutrient intake has been associated with a lower prevalence of chronic inflammatory diseases, and MUFA intake levels in particular are a predictive factor in psoriasis severity. (16)

Guselkumab is an IgG1 that blocks the p19 subunit of IL-23, is the first drug of its kind approved by the FDA on July 13, 2017, for the treatment of patients with mild to moderate plaque psoriasis. (17, 18)

The p19 subunit is specific for IL-23, selective inhibition of IL-23 may prove to be of great benefit, (19) as it is responsible for the differentiation and proliferation of Th-17 cells and thus in the production of Th-17-derived proinflammatory cytokines, including IL-17 and IL-22 (18), in addition to which IL-12-dependent functions remain intact, indeed IL-12 has been associated with inhibition of IL-17A-producing T-cell infiltration. (19)

For a patient to be a candidate for treatment, he/she must meet the criteria to be a candidate for systemic therapy or phototherapy (20).

The recommended dose of guselkumab is 100 mg orally in weeks 0 and 4, and subcutaneously once every 8 weeks after the fourth week (17, 18).

Some benefits of using this drug include a decrease in dendritic cells and T lymphocytes, as well as a decrease in the thickness of the affected skin at week 12 of treatment in biopsies performed on patients after its administration, and a reduction in IL-17 from the first week of treatment. A reduction in IL-17 was also demonstrated from the first week of treatment. (17) Currently the IL-23 and IL-17 axis are considered the most important pathogenic pathways in psoriasis. (19) This drug was compared with Adalimumab where the number of patients who obtained a PASI 100 with Guselkumab was superior. Of the patients who did not respond to Adalimumab, 66.1% responded when Guselkumab was administered. (17) It was also observed that Guselkumab improves symptoms of depression and anxiety, which are important comorbidities in patients with psoriasis compared to Adalimumab. (20) The NAVIGATE study made a comparison with Ustekinumab, it was found that 51.1% of patients treated with Guselkumab obtained a PASI of 90 compared to 24% for those treated with Ustekinumab. Patients who have not shown results with Ustekinumab at week 16 can be switched to treatment with Guselkumab showing clear improvement. Eclipse compared Guselkumab with Secunkinumab where its superiority was also demonstrated. Another advantage is that it is generally a well-tolerated drug. It was also shown to improve the quality of life of patients with psoriatic arthritis. (17) Another advantage is that it does not worsen Inflammatory Bowel Disease and has not been implicated in the development of Candida infections. (19) In addition to the physical benefits of the drug, its administration has also been shown to reduce absenteeism from work and school, since many of the

<table>
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<th>Table 1. Recommendations for combined therapies (13).</th>
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<tr>
<td><strong>Corticosteroids + Vitamin D</strong></td>
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<tr>
<td><strong>Mometasone furoate + salicylic acid</strong></td>
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<td><strong>Tazarotene + topical corticosteroids</strong></td>
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<td><strong>Dithranol + phototherapy or calcipotriol</strong></td>
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patients, as mentioned above, suffer from anxiety and depression. (20)
Adverse effects occurring in at least 1% of patients in the various studies included upper respiratory tract infections in 14.3%, headache in 4.6%, injection site reactions in 4.5%, arthralgia in 2.7%, diarrhea in 1.6%, gastroenteritis in 1.3%, ringworm in 1.1%, and herpes simplex in 1.1%. Migraine, yeast infections and urticaria occurred in more than 0.1% but less than 1% of guselkumab recipients.(18) Two cases of basal cell carcinoma, one of breast cancer and one of prostate cancer were found, these are no greater than those found with the use of other treatments.(17)

FORECAST
The disease tends to become chronic and in some cases is refractory to treatment. To evaluate the efficacy of treatment, a psoriasis activity and intensity index (PASI) (1) is used, aiming to achieve a PASI of 90, which means that there is a 90% reduction in the severity of the disease (11). The most important biomarker in prognosis is adiponectin (12).

DISCUSSION
Psoriasis is a chronic systemic inflammatory disease, in some cases difficult to treat. Treatment will depend on the clinical presentation, comorbidity, evolution and severity, subject to changes in dosage or medication.
In the Mexican CPG, topical corticosteroids, vitamin D analogues and tazarotene are considered first-line treatments, due to their few adverse effects and better response, and this coincides with other sources consulted (1, 6).
As a second line of treatment, systemic oral medications are recommended in all studies, which help when the first line medication fails, or in cases of moderate to severe psoriasis; however, it is important to take into account all the side effects they may cause, and the precautions to be taken with them.
However, Harrison mentions that TNF-alpha inhibitors can cause serious infections, hepatotoxic effects, congestive heart failure, hematologic episodes, hypersensitivity reactions, neurologic episodes, and most interestingly, the possibility of more cancers, David Fiorentino, one of the authors of Risk of malignancy with systemic psoriasis treatment in the Psoriasis Longitudinal Assessment Registry, differs, mentioning that this type of medication together with the anti-IL-12/23 antibody does not increase the risk of any type of malignancy in psoriasis, based on studies of case analyses of patients with no history of malignancy.
An example of the aforementioned is the selective inhibitor of the p19 subunit of IL-23, Gusekumab, a drug approved by the FDA in 2017, which was shown to be superior to other monoclonal antibodies used in current therapeutics, such as Adalimumab and Ustekinumab, because it proves to be beneficial in patients with moderate to severe psoriasis, because it not only improves the symptomatology but also decreases the IL-17A producing T cells in the skin and the promotion of an anti-inflammatory effect through the production of IFN-γ and IL-10, thus improving the quality of the patient and reducing the economic impact caused by the disease, since school and work absenteeism decreased in patients treated with this drug compared to other therapeutic schemes.
This drug has few adverse effects studied being so that only 1% present them, the most common are respiratory tract infections, which compared to those observed with other drugs are relatively mild. The only restriction is that it is only available in certain locations and it is currently not available in Mexico, so any benefit is in vain, and mainly because Mexico is a third world country and most of its population has low socioeconomic status, so it will not have the means to buy it from abroad and more because as it is a new drug, the price will be very high.
A long-term disadvantage of Gusekumab is the long administration time causing several patients to stop taking the drug, and the subcutaneous route of administration will cause long-term problems due to secondary discomfort at the site of application.
Despite all the research and novel therapeutics that can be used in psoriasis, it is still a disease of which several aspects are unknown regarding its etiopathogenesis (1), its comorbidities, and treatment remains difficult to manage because of its unpredictable course, and 52% of patients are not satisfied with their treatment. Biological treatments, considered the first choice (1), which have more specific targets than cyclosporine A or methotrexate, continue to have many adverse effects, including cancer, which often leads to decreased adherence.

CONCLUSION
Knowing the main manifestations and clinical presentations of psoriasis helps us to establish a timely diagnosis and provide the patient with better care, since, as we have seen, this disease is often accompanied by other pathologies that can reduce the quality of life of patients.
Research on new treatments and diagnostic methods will allow us to improve the patient’s prognosis because the books only present an outline that is old and it is necessary to be updated with new drugs and diagnostic methods, which will take several years to be found in a textbook. A clear example is to change eating habits, if we add to this an updated treatment, our patient will have satisfactory results.
Researching the benefits of new drugs helps us to provide the patient with an effective treatment with the least amount of adverse effects, this is the case of Gusekumab. The fewer adverse effects the drugs have, the more patients can achieve greater adherence and better control of the disease.

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