The Updated Guide in the Management of Psoriasis for Every Practitioner

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Abstract

Background: Psoriasis is one of the most common chronic cutaneous skin disorders, having genetic and immunological components. It is currently unknown what exactly triggers it, or how far reaching are the etiological factors, although great strides have been made in uncovering the pathophysiological cascade. Presently, there is a wide diversity of treatment methods for psoriasis, yet not all are applicable for each patient.

Methods: A non-systematic review of current treatment protocols for psoriasis, including topical, systemic, and biologic therapies, as well as phototherapy was performed.

Results and Discussion: Focal therapies such as topical agents and phototherapy are recommended for mild to moderate forms of psoriasis, whereas the severe or unresponsive forms are best treated via systemic or biologic therapies. Selection of both drug and dosage depends on both the knowledge and experience of the treating dermatologist, but also on the specific characteristics of each patient. Therefore, the treating physicians should be made aware of the management possibilities, their advantages, as well as their side effects.

Conclusion: In the following manuscript, we present an updated version of the commonly used therapies, alongside their indications, posology and most common side effects, a guide that may be useful for every practitioner in this field.

What is known:

- The current mechanisms for these therapies are known, as well as their clinical implications, indications, and adverse effects;
- There is currently a lack of comprehensive guides that explain both the mechanisms of action, indications, and posology for current treatment methods in psoriasis;

What is new:

- This review provides a detailed and comprehensive description for all these therapies and their pharmacodynamics, as well as the indications and adverse effects, making this a highly useful guide for any practitioner treating psoriasis;

Key words: Psoriasis; Immunosuppression; Topical therapies; Phototherapy; Systemic therapies; Biologic Agents

1. Introduction

Psoriasis is described as a chronic inflammatory pathology possessing substantial genetic and immunological constituents, and even though it primarily interests the teguments, it is irrefutably a systemic disease. Its most ubiquitous form is referred to as psoriasis vulgaris, the outpatients being commonly between the ages of 50 and 69 years old. Psoriasis concerns all races, with an international prevalence estimated currently at 100 million cases [1, 2]. It has an evolving characteristic, as well as the potential to severely encumber patients with through its underlying immunologic and inflammatory features [3]. The pathophysiological implications are convoluted and incompletely comprehended, yet it has been postulated that the psoriasis cascade is triggered by a genetic predisposition, in conjunction with a defective immune system and the implication of various environmental factors [4]. Despite the numerous progresses regarding our understanding and ability to control the evolution of the lesions, we are still only addressing the symptoms and the pathophysiological cascade, neglecting the actual causes of psoriasis. A large bulk of treatment methods is taken up by biological therapies, addressing the common elements of the pathological chain reaction that leads to the clinical manifestation. Nevertheless, the still bewildering task of deciding which treatment method is best suitable for each patient belongs to the practicing physician, mainly the dermatologist [5]. As such, individual care should be multidisciplinary, dermatologists also enlisting the assistance of psychologists and rheumatologists in order to impart the most fitting and affordable management choice, as well as the best possible long-term outcome.

2. Methods

We performed a non-systematic review of the literature, focusing on the most recent and updated data concerning topical, systemic, and biological therapies, as well phototherapy for psoriasis limited to the skin. Our aim was mainly to provide a comprehensive guide regarding the indications, benefits, posology, and adverse events for each of these treatment methods. To this purpose, we have considered relevant case reports and series, clinical trials, treatment-specific reviews, and even drug prescribing information.

3. Topical therapies

Topical therapy may be justified for mild to moderate forms of psoriasis wherein no more than 10% of the body surface is affected.

3.1 Dithranol, also known as anthralin or cignolin, exerts its effect by interfering with DNA synthesis, thus generating oxygen free radicals at the mitochondrial level. Concurrently, it decreases the activity of epithelial growth factor (EGF) and blocks the activity of prostaglandins, thereby diminishing keratinocyte proliferation and re-establishing the normal rate of cellular differentiation in the teguments. It is applied directly upon the psoriasis lesions in a concentration of 1%, maintained between 30 and 60 minutes and then thoroughly rinsed with water. An infrequent side effect is pseudoleukoderma. Both skin irritation and staining of the adjacent skin are more common adverse events. [6]

3.2 Salicylic acid is a topical keratolytic agent that interferes with the intercellular cohesion within the stratum corneum while also increasing the acidity at this level, subsequently reducing the intensity of scaling and softening the plaques. It can be used in concentration of 3-6% either incorporated into ointments or used as ready-mixed with propylene glycol in a 6% solution. Higher concentrations like 10% is suggested for use on the palms and soles. Among its adverse events, systemic absorption is by far the most important. While it can be safely administered during pregnancy, administration in children is discouraged [7]

3.3 Coal tar has been employed in the treatment of psoriasis for more than two millennia. It exerts its effects by diminishing the excessive proliferation of keratinocytes through DNA synthesis suppression. Coal tar has proven effectual upon several clinical forms of this disease, including chronic plaque psoriasis, scalp psoriasis, as well as palmoplantar psoriasis, ameliorating the aspect of the plaques after a month of therapy. It is used in concentrations of either 5% or 20%, or in combination with salicylic acid. Although the potential carcinogenic effect is the most dreaded, folliculitis at the site of application, staining and unpleasant smell are more common adverse events. [8]

3.4 Topical corticosteroids exhibit their effects via stabilizing and initiating nuclear translocation of glucocorticoid receptors, which represent components of the nuclear hormone receptor superfamily. In this manner, they reduce local inflammatory reactions, diminish keratinocyte proliferation and induce immunosuppression. Beneficial effects from local application occur after around 2 to 4 weeks after the first use. Corticosteroids serve as the first line of therapy in mild to moderate psoriasis, however prolonged exposure may lead to skin atrophy, telangiectasias, striations or a secondary infection. Whereas several clinical

studies have proven its safety in pregnancy, the administration in children under 2 years of age is advised against. [9]

3.5 Vitamin D analogues (calcitriol, tacalcitol, maxacalcitol, paricalcitol and becocalcidiol) interfere with keratinocyte vitamin D receptor and subsequently decrease cellular proliferation, inflammation and keratinization. Synchronously, vitamin D regulates the cellular differentiation process and inhibits the production of various proinflammatory cytokines such as IL-2 and IFN-γ. The application of calcipotriene 0.005% is recommended twice daily, with the caution of not exceeding the maximum dose of 100g/week. The only significant event related to topical vitamin D analogues is hypercalcemia. As such, vitamin D preparations are contraindicated in patients known with hypercalcemia or in pregnant women, yet allowed in children as long as the weekly dose does not surpass 50g. [10]

3.6 Calcineurin inhibitors (tacrolimus, pimecrolimus and sirolimus) carry out their effects by simultaneously blocking both IL-2 transcription and T-lymphocyte signal transduction, being utilized especially for the management of facial psoriasis and intertriginous psoriasis. Notable adverse events include burning sensation and contact dermatitis. They can be administered in children over 2 years of age. [9]

3.7 Tazarotene is a topical retinoid that connects with the receptors of retinoic acid found on cellular membranes, successively altering transcription processes in keratinocytes after being transported into the nucleus. Thus, it reduces cellular proliferation and stabilises epidermal differentiation, diminishing scaling and the thickness of plaques. It is found in the form of gels in concentrations of either 0.05% or 0.1%. When applied upon the fingernails, it ameliorates onycholysis, pitting and salmon patches. We mention local irritation as its most common side effect. It is contraindicated during pregnancy, yet safe to utilize in children. [11]

4. Phototherapy

The means in which phototherapy acts seemingly implicate the selective depletion of T cells, specifically those which are located in the epidermis. Apoptosis may be involved, as well as a shift in immunological response from Th1 to Th2 within the diseased skin (Figure 1).

4.1 UVB phototherapy is performed within the range of 290-320 nm, with the patient having to undertake between 2 and 5 sessions per week until either total remission is achieved, or no further improvements are observed upon the continuation of this therapy. Narrowband UVB (NB-UVB) realizes an emission of 312 nm and is apparently superior to conventional broadband UVB, treatment being offered 3 to 5 times a week. After 4

consecutive weeks since therapy initiation, a 70% improvement in the aspect of the lesions may be observed. Adverse effects number photodamage, photoaging, polymorphic light eruption, and potential carcinogenesis in the skin. [12]

4.2 Psoralen and Ultraviolet A Light (PUVA) is an immunomodulatory therapy that has been used in the management of psoriasis since the 1970s. The psoralen molecules interpolate in between DNA strands and, upon exposure to UVA, they generate adducts with the involved DNA, thereby limiting keratinocyte proliferation. Initial dose is 0.5–2.0 J/cm^2 of skin surface, depending on the individual's skin type. It is not recommended to participate in more than a total of 200 sessions during the patient's lifetime. A lesion remission may be observed in 70-90% cases. Among most notable possible side effects we mention photodamage, malignant melanoma and squamous cell carcinoma, as well as ocular damage. PUVA is discouraged in both pregnant women and in children under 10 years of age. [13]

4.3 Excimer LASER delivers supraerythemogenic doses of energy with a wavelength of 308 nm that can be delivered focally to affected skin, whilst sparing unaltered skin from avoidable exposure to radiation. The dosage must correspond to the individual phenotype and the thickness and induration of psoriasis plaques, adjustments being made in accordance to the response to therapy. The rate of success is around 70%, with two being the recommended number of sittings per week. It is especially useful for recalcitrant plaques located at the elbows and knees. As common side effects erythema, blisters, hyperpigmentation and erosions are noted. [14]

5. Systemic therapies

Since they possess high efficacy, systemic therapies are advocated for severe forms of psoriasis, serving their role by modulating the functions of T cells.

5.1 Methotrexate (MTX) is a folic acid analogue that exercises its effect by inhibiting an enzyme involved in purine metabolism, namely 5-aminoimidazole-4-carboxamide ribonucleotide transformylase, thus generating an accumulation of extracellular adenosine known for its potent anti-inflammatory properties. One can expect the outcome of MTX therapy to appear 4 weeks from the first dose. The weekly dose should not exceed 15-25mg in total, with the recommended concomitant intake of folic acid (1-5 mg/day) to reduce certain adverse events such as nausea or megaloblastic anaemia. MTX clearance is obtained via renal excretion, therefore its usage is contraindicated in patients with renal impairment, especially considering that side effects are generally dose related. Additionally, great care must be given towards individuals with pre-existing hepatopathies or those suffering from

chronic alcoholism, diabetes mellitus, hyperlipidaemia or obesity, a liver biopsy being highly recommended before starting therapy in these patients. In the event either medullary toxicity or overdosage is suspected, an oral or parenteral dose of leucovorin calcium 20 mg is immediately given, then repeated every 6 hours as required. The most common side events are myelosuppression, hepatotoxicity, pneumonitis, mucosal erosions, diarrhoea, bleeding, anagen effluvium, and inhibition of spermatogenesis. Intuitively, this drug is not permitted during pregnancy and whilst breast feeding due to its grim teratogenic effects. Therefore, the use of effective contraception is highly advocated in the course of MTX treatment. [15]

5.2 Cyclosporin A is a calcineurin inhibitor that acts by impeding the synthesis of IL-2 by T cells, thereby abruptly obstructing the cytokine cascade. Cyclosporin is effective especially in patients with severe or extensive forms of psoriasis, even erythrodermic psoriasis. Recommended starting dose is 2.5 mg/kg daily, a dose which can be maintained if the skin aspect has recovered after one month of treatment. Should there be no clear amelioration of the psoriasis lesions, the dose may be increased up to 5 mg/kg daily. Nevertheless, the total length of therapy with Cyclosporin must not surpass one year, according to recommendations. It is imperative that the renal functions in these patients is monitored, since Cyclosporine is nephrotoxic and can engender permanent renal damage. If the serum creatinine levels increase by more than 30% of the initial value, therapy may be discontinued. Tremors, headache, paraesthesia or hyperesthesia, gingival hyperplasia, hypertrichosis, as well as cutaneous malignancies are mentioned as possible side effects. [16] Furthermore, Cyclosporine treatment ought to be avoided while pregnant because of the presumed roles calcineurin inhibitors play during neural development in the embryo and foetus. Concurrently, Cyclosporine in pregnancy should utilized only in the scenario that the treatment benefits justify the hypothetical teratogenic risks. [17]

5.3 Fumaric acid esters are utilized in the management of psoriasis, despite its presently unclear action mechanism. It seems that after interacting with intracellular reduced glutathione, they inhibit the nuclear translocation and the transcriptional activity of the nuclear factor kappa-light-chain-enhancer of activated B-cells. Initiation therapy is recommended with a low dose, which can later be increased thusly: in week one, one tablet of 30 mg is recommended per day, followed by two daily tablets of 30 mg in week two, and then three 30 mg tablets each day in the third week. From week four and beyond, the patient may take just one tablet of 120 mg in the evening. According to the response to therapy, the daily dose may be further heightened, with the caution of not surpassing 720 mg (six tablets per day). If the patient exhibits a stable remission of psoriasis lesions, the maintenance dose

can be lowered until the individual's threshold is attained. Among the most common side effects, we count eosinophilia, which regularly occurs within the first week from therapy initiation, reversible lymphopenia, flushing, nausea, and vomiting. Its administration in patients suffering from malignancies or in pregnant women is discouraged. [15, 18]

5.4 Acitretin embodies a second-generation retinoid that is administered specifically for the treatment of generalized pustular and erythrodermic psoriasis. Currently, the mechanism through which it exerts its effects is not fully elucidated. The ideal starting dose of acitretin in psoriasis has been conveyed at 25 mg/day, while the maintenance dose stands between 20 to 50 mg/day. Apparently, after approximately 60 days after cessation of therapy, most of the individuals experience relapse. Among the reported adverse events we cite xerostomia, xerophthalmia, rhinitis sicca eyes, hair loss, paronychia, dyslipidaemia, hepatotoxicity, arthralgia, and even pseudotumor cerebri. The increased teratogenic potential of retinoids sternly constrains their usage in women seeking pregnancy who should receive proper guidance on the means and importance of contraception. Additionally, pregnancies should be avoided for at least three years after cessation of Acitretin therapy, with pregnancy tests being performed every three months in the course of treatment. [19]

5.5 Apremilast is used in treating psoriasis because its capability of inhibiting phosphodiesterase (PDE)-4, which itself breaks down intracellular cyclic adenosine monophosphate (cAMP), thus accumulating larger amounts of intracellular cAMP while also inhibiting NF-κB signalling. Furthermore, it increases the expression of anti-inflammatory cytokines such as IL-10. In order to reduce the risk of gastrointestinal symptoms, the administration dose is titrated along the first week, starting with a 10 mg tablet in day one so that by day 6 we are able to administer a tablet of 30 mg twice daily, which will also represent the maintenance dose for the remainder of the treatment. Side effects include diarrhoea, nausea, vomiting headache, and weight loss. [15, 20]

5.6 Tofacitinib is taken orally and epitomizes a Janus kinase inhibitor, thereby playing a role in the downstream signalling of several proinflammatory cytokines such as IL-2, IL-4, IL-6, IL-9, IL-13, IL-21, as well as the signalling cascade of type I and II IFN. To a lesser degree, it also affects IL-12 and IL-23. For the time being, Tofacitinib is approved only in rheumatoid arthritis, however various finalized clinical trials have validated its effectiveness in psoriasis, with promising results when administered in doses of either 5 mg twice each day or 10 mg twice each day. Being an immunosuppressor, it is crucial that all patients are tested for tuberculosis before initiating therapy, whereas during treatment their haemoglobin,

leucocyte and serum lipid levels are routinely monitored. The heightened risk of developing infections is the most important adverse event. [21, 22]

5.7 6-Thioguanine is a purine analogue predominantly designated for acute myelogenous leukaemia that has nonetheless demonstrated its efficiency in the treatment of severe refractory psoriasis as well as palmoplantar pustular psoriasis. It acts out by transmuting into 6-thioguanosine monophosphate, which accumulates within the cells and impede the production of guanine nucleotides through inosine monophosphate dehydrogenase. It is recommended to start therapy with 40 mg/day a dose which can be increased up to 60-80 mg/ day along several weeks. Once remission is achieved, a maintenance dose of 40 mg given every two days or twice per week. [23] Due to its effectiveness, 6-Thioguanine should be considered for individuals who have failed to adequately respond to other systemic agents. Among adverse effects, the most worrisome is myelosuppression, yet hepatotoxicity, nausea, vomiting, diarrhoea, as well as skin malignancies. However, additional prospective studies are required to augment the effectiveness of this agent and minimalize toxicity in the treatment of psoriasis. [24]

5.8 Mycophenolate Mofetil derives from mycophenolic acid, diminishes guanosine nucleotides specifically in T and B lymphocytes while also hindering their proliferation, thus repressing cell-mediated immune responses and generation of antibodies. Recently it has been recommended for the management of psoriasis for cases who are otherwise unfit for other existing agents. [25] As reported by recent studies, a reduction in the PASI score of at least 47% was registered in patients taking 2g/day of mycophenolate mofetil. [26] It is ordinarily well tolerated with few common side effects such as constipation, headache, nausea, vomiting, and loss of appetite. [25, 26]

6. Biologic therapies

During the last few years, numerous achievements have been made in apprehending the complex physio- pathological mechanisms of psoriasis. However, the precise contrivances of this process are still poorly defined, although it seems that prior to a slight trauma, the myeloid dendritic cells initiate an amplified production and secretion of interleukins, for instance IL-12, IL-23 and TNF- α, which act as chemoattractants for the T helper Th-1 and Th-17 cells [27]. Understandably, targeting these interleukins would lessen the severity of the disease by interrupting the pathophysiological cascade near its onset (Figure 2).

6.1 TNF-α inhibitors represented by adalimumab, etanercept, infliximab and certolizumab. These agents specifically hinder the TNF-α signalling pathway, considerably lessening the severity of the inflammatory process [28]. Adalimumab was derived from phage display and it is a fully human monoclonal antibody. [29] It is administered subcutaneously once every two weeks [30]. Etanercept, on the other hand, represents a dimeric fusion protein fabricated via recombinant DNA techniques, embodying a total of 934 aminoacids. As stated by Haraoui B et al., etanercept performs akin to a natural antagonist, basically hampering the circulating TNF α and β from adhering to their respective receptors on the surface of target cells in a competitive manner. [31] It is administered subcutaneously once a week. [32] Infliximab is a chimeric monoclonal IgG1 antibody that has both a human and a murine part. It connects to the soluble subunit and the membrane-bound precursor of TNF-α, consequently interfering with the interaction between TNF-α and its specific receptors, and thereupon instigating the lysis of the cells producing TNF-α [33]. It is administered intravenously once every 8 weeks. [34] Certolizumab is a monoclonal antibody augmented by pegylation, which does not include the Fc portion, this having the purpose of precluding complement binding and antibody-mediated cytotoxicity, as well as to drastically increase its half-life [35]. Its administration is subcutaneous, either 200 mg every 2 weeks or 400 mg every 4 weeks, and it can also be safely administered in pregnant women [36, 37]. Table I shows the exact posology for each of the anti TNF-α agents and the adverse effects [38-41].

Table I. Anti TNF-α Agents. Posology. Adverse events

TNF-α inhibitor	**Administration**	**Adverse events**
Adalimumab	40 mg x 2 at week 0, afterwards 40 mg x 1 administered every 14 days	Upper respiratory infections, rash, urinary tract infections, angioedema, anaphylaxis, dyspnoea, liver toxicity hypotension, cardiac failure serum sickness, urticaria, lymphomas or other malignancies, reactivation of the tuberculosis or hepatitis B virus, pain, swelling, haemorrhage or erythema at
Etanercept	50 mg x 1 twice a week during the induction phase (the first three months), thereafter only one injection weekly	
Infliximab	5mg/kg are administered via intravenous infusion at weeks 0, 2, 6 and after that	

	every 8 weeks.	the injection site, demyelinating central nervous system disorders, pancytopenia, including aplastic anaemia
Certolizumab	200 mg x 2 at the start of therapy at Week 0, Week 2, and Week 4 and 200 mg once every 2 weeks (or 400 mg once a month)	

Adalimumab is also indicated for sever plaque psoriasis in children over 4 years and teenagers who did not respond accordingly to or were otherwise ineligible for topical drugs or phototherapy [38]. The recommended dose for both original and biosimilar forms of adalimumab is 0.8 mg/kg of body weight (up to a maximum 40 mg per single dose) admistered via a weekly subcutaneous injection for the first two doses, and only once every two weeks for each subsequent dose. For children with a body weight of 15-30 kg, the initial induction dose of 20 mg, followed by the ensuing 20 mg dose every two weeks starting from the second week of treatment, whereas children over 30 kg receive 40 mg doses in the same fashion.

Etancercept can also be given to children over 6 years, with the recommended dose of 0.8 mg/kg of body weight (though no more than 50 mg per dose) once a week [39].

Drug interactions. Several reports have stated that other biologic therapies, live vaccines, ankinra, abatacept interact with TNF-α inhibitors. The FDA has sanctioned certolizumab as non-toxic and safe to use throughout pregnancy. Current information does not convey either supplementary teratogenic events in comparison with the general population, or a heightened chance of causing death to the foetus [37]

6.2 IL-12/23 inhibitors are portrayed by ustekinumab, guselkumab, and tildrakizumab. Il-23 is a heterodimeric cytokine that incorporates two subunits: the p19 subunit, which is interconnected to the p40 subunit, this latter one being also shared with IL-12. Il-23 is the main character that prompts the activation of the T-helper 17 inflammatory pathway, whereas IL-12 enacts the chief role in Th-1 differentiation and proliferation. Ustekinumab is a human immunoglobulin G1 kappa monoclonal antibody whose antigen-binding fragment attaches to the D1 domain of the p40 subunit of IL-12 and IL-23, thus preventing both of these cytokines from interacting with their receptors, and ultimately leading to the concurrent suppression of the Th1 and the Th17 inflammatory cascades [42]. It is administered subcutaneously once every 12 weeks following the induction phase.

Guselkumab is a fully human antibody, a G1 type of immunoglobulin, that binds to the p19 subunit of IL-23, consequently deterring the IL-23/IL-17 axis, which is according to current evidence the main pathogenic pathway within psoriasis. [43] It is delivered subcutaneously once every 8 weeks. Tildrakizumab stands for a high-affinity humanized antibody that distinctively targets IL-23p19, hence impeding the IL-23/Th17 pathway that progresses a potent inflammatory response. [44] It is given subcutaneously every 12 weeks succeeding the induction phase. Risankizumab represents another fully humanized IgG monoclonal antibody that targets with elevated affinity the p19 subunit of IL-23. By inhibiting IL-23, risankizumab lessens the differentiation of TH-17 and TH-22 cells, hereafter obstructing the main inflammatory cascade resulting in the production of IL-17. [45] It is delivered by subcutaneous injection every 12 weeks, following the induction phase. Table II presents the posology and adverse events for this anti-IL-12/23 biological agents. [46-49]

Table II. IL-12/23 Inhibitors. Posology. Adverse events

IL-12/23 inhibitors	**Administration**	**Adverse events**
Ustekinumab	45 mg x 1 at weeks 0 and 4 and at every 12 weeks subsequently	Infection and infestations such as tinea infections, Herpes simplex infections, reactivation of tuberculosis, malignancies, hypersensitivity reactions, headache, fatigue, injection site reaction, joint pain, and gastroenteritis, rash, urticaria
Guselkumab	100 mg x 1 administered at weeks 0 and 4 followed by a maintenance dose every 8 weeks.	
Tildrakizumab	100 mg x 1 at weeks 0, and 4 and every 12 weeks thereafter.	
Risankizumab	75 mg x 2 at week 0, week 4, and every 12 weeks thereafter.	

Ustekinumab lends itself for administration in children older than 6 years who did not show a satisfactory to therapy. The sanctioned dose of Ustekinumab is adapted to body weight. It is given in weeks 0 and 4, then every 12 weeks. A dosage of 0.75 mg/kg is indicated for children under 60 kg, for those between 60-100 kg a total dose of 45 mg, whereas those over 100 kg a 90 mg dose is recommended [46].

Drug interactions. According to Gupta et al., IL-12/23 inhibitors do not seem to impact the pharmacokinetics of associated medication metabolized by the CYP enzyme, but it has been noticed they might interact with live vaccines [50].

6.3 Chief among IL-17 inhibitors stand ixekizumab, secukinumab and brodalumab. IL-17 is a cytokine family comprised of six members: IL-17A, IL-17B, IL-17C, IL-17D, IL-17E, IL-17F, and they appear to possess a key role in the pathogenesis of psoriasis and other immune-mediated diseases owing to their capability of activating inflammatory responses in several tissues and organs [51]. Being generated by the T helper 17 cells (Th-17), IL-17A is currently the most attentively studied cytokine mainly since it is a principal actor in the inflammation process, neutrophil recruitment and host defence mechanisms [52]. Ixekizumab is a humanized IgG4 monoclonal antibody that binds with high affinity to IL-17A/F heterodimers, neutralizing their proinflammatory effect. [53] It is given subcutaneously every 4 weeks, succeeding the induction phase. Secukinumab epitomizes a fully human IgG1 monoclonal antibody that prevents with high specificity the action of IL-17A, thereby inhibiting keratinocyte activation as well as the production of inflammatory mediators [54]. It is delivered subcutaneously every 4 weeks, following the induction phase. Brodalumab is a fully human IgG2 monoclonal antibody that attaches with increased affinity to the IL-17 receptor A, a receptor that is mutual to IL-17A and other IL-17 cytokines, rendering its effect wider although more unspecific [55]. Table III presents the posology and adverse events for this anti-IL-17 biological agents [56-58]

Table III. IL-17 Inhibitors. Posology. Adverse events

IL-17 inhibitors	**Administration**	**Adverse events**
Ixekizumab	80 mg x 2 at week 0 then 80 mg at weeks 2, 4, 6, 8, 10 and 12 and at every 4 weeks subsequently	Serious infections, headache, joint pain, hypertension and major cardiovascular events (e.g cardiac failure), diarrhoea, injection site reaction (oedema, pain, erythema, ecchymosis), musculoskeletal pain, hypersensitivity reactions, neutropenia
Secukinumab	150 mg x 2 at weeks 0, 1, 2, 3, 4 and after the induction phase, 150 mg x 2 at every 4 weeks	
Brodalumab	210mg x 1 at week 0, 1 and 2 followed by 210 mg x 1 every 2 weeks afterwards	

Drug interactions. Il-17 inhibitors may interact with medication metabolized by cytochrome P450, such as warfarin, caffeine, omeprazole, metoprolol, midazolam, cyclosporine and so on [59].

7. Conclusions

Even though in recent times the treatment of psoriasis has experienced numerous breakthroughs, we are still far from actually curing this chronic illness. It is important to adjust therapeutic methods according to the individual characteristics of each patient and their diseases. Mild to moderate forms of psoriasis may benefit especially from topical therapies. Topical therapy for psoriasis vulgaris is adapted to the topography of affected body areas: for hairy skin (such as the scalp), pharmaceutical forms like gels (calcipotriol and dermatocorticoid combinations) or lotions/solutions (calcipotril, dermatocorticoids) are advised. Systemic agents are generally reserved for the moderate-to-severe forms, with the latter possibly obtaining a PASI 75. Furthermore, a PASI 100 can only be achieved via biologic therapies. The experience of dermatologists and the characteristics of each patient should guide us toward the selection of the most appropriate and advantageous form of treatment.

Conflicts of interest

The authors have no conflicts of interest to report.

Ethical statement

This manuscript was exempt from ethical review, since it does not involve human or animal studies and is a review of the literature.

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Figure 1: The pathophysiological process in psoriasis is initiated by triggers acting at the skin level, determining the activation of the plasmacytoid dendritic cells and their transformation into dermal dendritic cells. Anti-TNF-a therapies block the inflammatory process from its early stages.

Once activated, dermal dendritic cells increase IL-23 and IL-17 signalling on several immune cell populations. Activated Th17 cells produce key cytokines such as IL-17, IL-22, IL-26 and IL-29. During this stage, anti-IL-17 agents like ixekizumab, secukinumab and brodalumab suppress the inflammatory cascade and its offshoots.

On the other hand, IL-23 promotes clonal expansion and differentiation of Th22 cells that produce IL-22, in turn altering keratinocyte differentiation and proliferation. The action of drugs such as Guselkumab, Tildrakizumab and Risankizumab on IL-23 regulates these processes, thereby normalizing cellular turnover.

IL-12 produced by the activated dermal cells, as well as keratinocyte-derived CXCL9/10/11, stimulate the influx of Th1 cells within the damaged skin, leading to important pro-inflammatory effects. It is at this stage that Ustekinumab acts, hindering IL-12 and concurrently reducing skin inflammation significantly.

Figure 2: Following the action of triggers at the skin level, plasmacytoid dendritic cells are activated and metamorphose into dermal dendritic cells. These in turn increase IL-23 and IL-12 signalling, leading to the activation of Th17 and Th1 respectively, causing the release of several proinflammatory cytokines responsible for the clinical manifestations in psoriasis.

Phototherapy seems to down-regulate the Th1/Th17 proinflammatory axis, while also heightening the Th2 cell population, which results in an important clinical improvement.