The Actual State of Psoriasis Therapies

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INTRODUCTION

Psoriasis **(Ps)** is an autoimmune, chronic inflammatory skin disease affecting around a total of 2% of the general population in Europe and North America [1]. Ps is considered to be a multifactorial disease, in which the genetic background interacts with environmental factors to define the individual's risk [2].

The classical clinical manifestations of Ps are well demarked as the presence of red, infiltrated plaques, covered with a coarse silvery scaling (Figure 1,2). Predilection sites include elbows and knees, the scalp, and per umbilical and lumbar regions, but psoriasis can affect any anatomical site, even at the same time [3]. The clinical course of Ps is marked by frequent relapses with very fluctuating rates [1]. Psoriasis Area and Severity Index **(PASI)** is the most widely used score in psoriasis trials. The main goal in psoriasis treatment, according to a European consensus statement, is to reduce the total amount of cutaneous signs and symptoms by at least a 75% as measured by the PASI score, and to guarantee a good quality of life, as measured by a Dermatology Life Quality Index **(DLQI)** score of 5 or less [4].

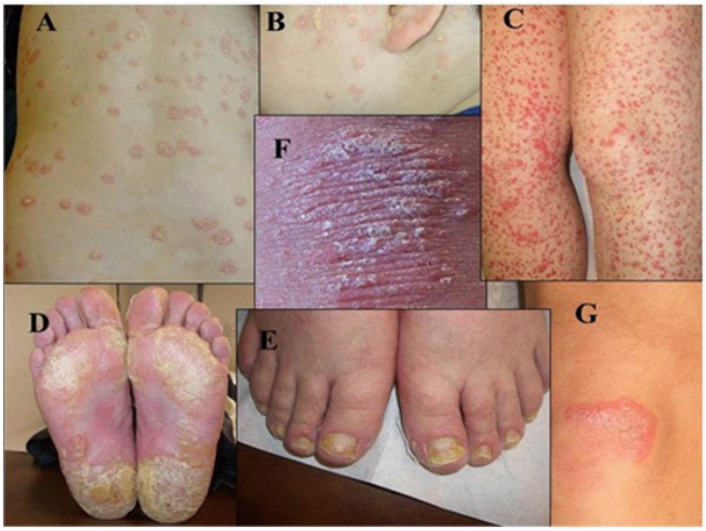

Figure 1: A,B; Guttate psoriasis: Small, dot-like erythematous scaling lesions triggered by a strep infection. C; Psoriasis induced by drugs: Multiple eruptive sharply demarcated erythematous round patches. D; Psoriasis involving the hands and feet affects about 30% of patients with plaque psoriasis. E; Nail changes occur in up to 50% of people with psoriasis. F,G; Plaque psoriasis: the most common form: raised, red patches covered with a silvery white scale on the knees and elbows.

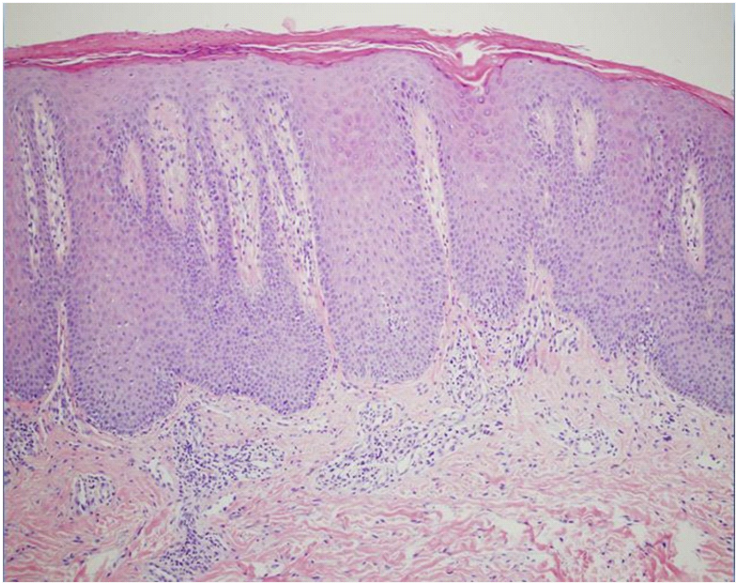

Figure 2: A biopsy show (Hematoxilin/eosin x 100): Parakeratosis (cell nuclei within stratum corneum), agranulosis (no granular layer), psoriasiform hyperplasia (thickened projections of the cell layer or keratinocytes), polymorphonuclear leukocytes and lymphocytes infiltrate and blood vessel dilation in the dermis.

While recent advances and investment in high-cost biological therapies have revolutionized outcomes for patients with severe disease, comparatively little attention has been paid to topical therapy, which forms the cornerstone of management for the majority of people with psoriasis [5]. It is estimated that moderate-to-severe psoriasis accounts for about a 25% of the total psoriatic patients [6], most of whom are likely to require the use of systemic drugs or phototherapy. Long-term management of psoriasis requires an individualized approach. Rotational and combination treatments are practical strategies commonly used in clinical setting to reduce the cumulative toxicity of anti-psoriasis treatments and to optimize their risk/benefit ratio.

For decades, the treatment of Ps has been directed toward the improvement of the skin manifestations with topical preparations, phototherapy, and systemic medications (such as Methotrexate, Cyclosporine, or Retinoids). The introduction of monoclonal antibodies (biological drugs) that selectively block the proinflammatory cytokine Tumor Necrosis Factor **(TNF)**, such as Adalimumab, Etanercept and Infliximab, has revolutionized the treatment of Ps and other immune-mediated inflammatory diseases [7]. These agents have improved the prognosis of Ps markedly and therefore the number of patients under these treatments is increasing, but they are expensive and this represents a major concern for the health systems [8]. Currently Ps causes remarkable direct costs, work limitations and productivity loss [9]. Psoriatic patients incurred incremental medical costs of 2284$, experienced a 2203$ reduction Health-Related Quality of Life **(HRQOL)**, and a 1935$ reduction in productivity. The total burden of psoriasis was estimated as 35.2$ billion, with 12.2$ billion in incremental medical costs (35%), 11.8$ billion from reduced HRQOL (34%), and 11.2$ billion from productivity losses (32%) [10]. The patients with severe disease report higher levels of absenteeism and changes in employment status as result of Ps, which explains their higher total indirect costs compared with the other PASI groups [11]. A literature review of systemic psoriasis treatments that have been approved by the FDA was performed for the primary end point of a 75% reduction in the Psoriasis Area and Severity Index score **(PASI 75).** Methotrexate (794.05-1502.51$) and Cyclosporine (1410.14-1843.55$) had the lowest monthly costs per NNT to achieve PASI 75. The most costly therapies were infliximab (8704.68-15,235.52$) and ustekinumab 90 mg (12,505.26-14,256.75$). Monthly costs per number needed to treat to achieve PASI 75 for other therapies were as follows: Narrow Band Ultraviolet B light Phototherapy (2924.73$), Adalimumab (3974.61-7678.78), Acitretin (4137.71-14,148.53$), Ustekinumab 45 mg (7177.89-7263.99$), Psoralen plus Ultraviolet A light Phototherapy (7499.46-8834.98$) and Etanercept (8284.71-10,674.89$) [12]. The cost of biologic treatments for psoriasis has been increasing over the time and the cost factor must be considered when evaluating the diverse management options for psoriasis [13].

PSORIASIS THERAPY

The psoriasis guidelines include topical therapies (glucocorticosteroids and vitamin D derivatives); phototherapy (ultraviolet B exposure, Psoralen plus ultraviolet an exposure);

conventional (Acitretin, Cyclosporine and methotrexate) and biological systemic therapies (Anti-Tnf-α, Etanercept, Adalimumab, Infliximab; Anti-interleukin 12/23 Ustekinumab; Anti-interleukin-17A: Secukinumab; Phosphodiesterase inhibitors: Apremilast) (Table 1).

Table 1: Anti-psoriatic therapies. Modified from [53,91,92]. Efficacy: Estimated proportion of patients who achieved at least a 75% reduction in their PASI.

	Efficacy	Level of evidence
Topical therapies		
Glucocorticosteroids	50-60% [93,94]	1
Vitamin D derivatives	40-45% [16]	1
Phototherapy		
Ultraviolet B exposure	70%-80% [23,95,96]	2
Psoralen plus ultraviolet A exposure	80%-90% [23,96]	2
Conventional systemic		
Acitretin	15-40% [41,97,98]	3
Ciclosporin	50-70% [53,91,92]	1
Methotrexate	50%	2
Biological		
Apremilast	30% [99]	1
Adalimumab	70% [67,69]	1
Etanercept	40-60 % [56-58]	1
Infliximab	75-80%	1
Ustekinumab	70%	1
Secukinumab	80% (77)(76) [76,77]	1

Topical Therapies

Most patients with psoriasis have skin lesions limited to localized areas. For these patients, topical therapy may remain as the main therapeutic regimen. Topical Corticosteroids **(TC)** are the most widely prescribed medications for plaque Ps. They are available in numerous vehicles. Different preparations are used on various body sites [14]. One of the most troubling features of topical corticosteroids is that patients develop tachyphylaxis, (medications that are highly effective initially, but loose they efficacy with a prolonged use).

The second most commonly used group of topical medications is the vitamin D analogues; these agents are applied once or twice daily and can be used in conjunction with TC. The following expert recommendations for the topical long-term treatment of psoriasis with vitamin D3 analogues and their combinations have been published: A) Patients should be proactively involved in the choice of treatment, formulation and mode of application. B) Besides long-term treatment with the two-compound-formulation other treatment regimens including calcipotriene mono therapy can also be considered. C) Due to the favorable risk-benefit ratio observed in maintenance trials and due

to better cost-effectiveness the application of two-compound-products once or twice a week after initial therapy is recommended [15]. Vitamin D analogues perform at least as well as TC, and they are associated with a low incidence of local adverse events [16].

PHOTOTHERAPY

Phototherapy is one of the most efficacious treatment options for Ps. Four categories of action were proposed in the medical literature to describe the effects of phototherapy in psoriasis: 1) Alteration of cytokine profile, 2) Apoptosis induction, 3) Promotion of immune suppression 4) Other mechanisms [17,18].

Phototherapy is now one of the most common treatment options for psoriasis. Treatment algorithms for Ps recommend the use of phototherapy before the use of systemic agents because of the proven safety, efficacy, and low cost of phototherapy [19]. Established photo therapies include the widely used narrow-band UVB (ultraviolet B) and—to a lesser extent—photo chemotherapy such as Psoralen Plus Uva, Ultraviolet A **(PUVA)** [20]. For optimal effect, patients are usually treated 2-3 times per week for several months. The pooled effect estimate of the efficacy (PASI 75) of topical PUVA, targeted UVB, was as follows: 77% (topical PUVA), 61% (targeted UVB). Topical PUVA and targeted UVB phototherapy are very effective in the treatment of localized psoriasis [21]. Technological innovations involving the development and improvement of ultraviolet-emitting devices designed for home phototherapy have widened the possibilities for home [22], The phototherapy use of Ps patient satisfaction with home phototherapy is very high [23].

The risk of non-melanoma cutaneous malignancies increases with the number of treatments but are rare in dark skinned patients [24]; then the carcinogenic potential of PUVA limits its long-term use. Patients with moderate to severe psoriasis indicated clear preferences for oral therapies (e.g. Methotrexate) over Phototherapy (e.g. PUVA) [25].

CONVENTIONAL SYSTEMIC TREATMENTS

The three approved conventional systemic treatments for psoriasis are: Methotrexate, Acitretin, and Cyclosporine. Their use, advantages, and disadvantages, are discussed below.

Methotrexate

Methotrexate **(MTX)** remains the most commonly prescribed drug worldwide in Ps. This drug has been the standard systemic mono therapy for psoriasis for over five decades, and is still considered the gold standard, even with the advent of biological drugs [26]. The US Food and Drug Administration **(FDA)** approved the use of MTX for the treatment of psoriasis in 1972 [27]. Guidelines regarding the dosing regimen for MTX are partially based on expert opinions [28] and vary in their recommendations. In daily clinical practice the patients with psoriasis are often undertreated [29]. A recent systematic review highlights the wide heterogeneity in MTX dosing regimens, such as the use of a test-dose, start-dose, dosing scheme, dose adjustment, maximum

dose and folic acid (FA) supplementation [30]. Based on the review the authors made suggestions for several aspects of the MTX use (Table 2).

Table 2: Suggestions for methotrexate dosing regimen [30].

Test dose: Recommended for elderly or frail patients.
Start dose: 15 mg/week in healthy patients; 5-7.5 mg/week in elderly or frail patients.
Administration as single dose.
Dose increase at week 8-20mg/week if an insufficient response is seen.
Maximum dose of 25mg/week.
Folic acid is recommended (1-5 mg/daily).

The most commonly reported side effects are mild and include some gastrointestinal complaints, such as nausea, vomiting, and diarrhea. Hematologic complications are the major cause of death related with this therapy, and may be manifested as anemia, leukopenia, thrombocytopenia, or pancytopenia. Renal insufficiency, increased means corpuscular volume, age, and drug interactions are predisposing risks factors. Hepatotoxicity is also a concern so the drug should be avoided in current or previous liver disease patients. Patients should be counseled to avoid alcohol and have routine monitoring of liver function tests [31-33]. Findings suggested that there is no increased risk of onset of lung disease in methotrexate treated patients with non-malignant inflammatory diseases [34]. MTX has multiple drug interactions; therefore, prior to initiating therapy, a thorough review of the patient's medications is essential [35]. MTX is likely to remain a useful adjunctive therapy to newer treatment options such as biological drugs [26].

Cyclosporine

The first observations documenting the clinical activity of Cyclosporine A **(CsA)** oral in Ps have passed more than 30 years [36]. A considerable amount of clinical data has been accumulated in favor of the efficacy and safety of this drug in Ps. At the light of the current knowledge and after several years of experience gathered in clinical practice, CsA is often used as first-line therapy in moderate-to-severe forms of Ps by several dermatologists. Ps treatment regimens with CsA have to be adapted to the patient's needs and specific characteristics, after an accurate selection and a careful assessment of the risk/benefit ratio [37]. CsA has the highest efficacy among all the non-biologic systemic therapies. It is called the "crisis drug" because it is effective in cases resistant to other modalities and brings a quick control even in very severe cases. CsA is given in doses of 2.5-5 mg/kg/day. Dose and duration of CsA treatment are generally tailored to the patient's general characteristics and specific needs and should be adjusted throughout the treatment course in accordance with individual efficacy and tolerability [38]. Main problems with CsA are drug-induced hypertension, renal side effects, increased incidence of malignancy and rebound flare after stopping the drug [39]. A recent systematic review with over 25 years of dermatologic experience worldwide does not clearly substantiate that the skin cancer risk would be necessarily increased in patients using CsA for cutaneous diseases, unlike that this complication can occur in organ transplant recipients [40].

Acitretin

Acitretin, the active metabolite of Etretinate, is the most commonly used oral retinoid for psoriasis. Acitretin is a vitamin A derivative, which modulate epidermal proliferation and differentiation, has immune modulatory as well as anti-inflammatory properties. It is less effective compared to MTX and CsA as monotherapy and requires 3-6 months of duration of treatment before achieving a maximal response. It has been used in different doses in clinical trials and the results are largely dose dependent [41,42]. Starting daily dosages between 10 and 25 mg and stepwise escalation were associated with higher clinical efficacy and lower incidence of adverse events in comparison with higher doses and regimens rapidly reaching optimal dose [43]. The clinical efficacy of Acitretin depends clearly on the clinical type of Ps. Erythrodermic and pustular Ps forms; exhibit a good response to Acitretin, while the drug is only moderately efficacious in chronic plaque-type Ps [44].

An important difference between Acitretin and other systemic treatments is the different effect on the immune system and therefore the different side effects. This could be an argument to choose Acitretin over the other systemic therapies in specific patient populations: immune compromised patients, patients prone to infections, patients with a history of high cumulative doses of UV or other patients with an increased risk of skin malignancies [45]. For patients with psoriasis and HIV infection when systemic therapy is indicated, Acitretin is the drug of choice [46].

Side effects are very common and dose limiting, but they can be minimized by appropriate patient selection, careful dosing, and monitoring [44]. Side effects are related to vitamin A toxicity, conjunctivitis, alopecia, photosensitivity, hyperlipidemia, muscle-, joint-, and bone pain, retinoid dermatitis, hyperostosis (irreversible), gastro-intestinal complaints, hepatitis, jaundice, idiopathic intracranial hypertension, decreased color vision and impaired night vision [41].

Acitretin is a pregnancy category X drug. Major human fetal abnormalities associated with retinoids include myelo-meningocele, meningo-encephalocele, multiple bone malformations, facial dysmorphia, low-set ears, high palate, anophthalmia, abnormalities of appendages including syndactyly and absence of terminal phalanges, malformations of the hip, multiple synostosis, decreased cranial volume alterations, and cardiovascular malformations [47]. Two forms of effective contraceptives should be used, beginning one month prior to starting Acitretin, throughout the duration of treatment and for 2 years in Europe and 3 years in US after stopping [41].

It is recommended to monitor the liver function tests, the fasting serum cholesterol and triglycerides and the blood sugar (in diabetics) every 2-4 weeks for the first 2 months of therapy and after that period every 3 months during all time period of treatment [48].

BIOLOGICS

Current European and British Treatment Guidelines still recommend the use of biologic agents as the third-line choice treatment (Table 3). Etanercept and Adalimumab are recommended above infliximab as first-line biologic therapy [49,50]. A clear ranking of the available treatments is not yet possible [51]. A 2011 meta-analysis evaluated the randomized controlled trials published up to 2008 comparing the efficacy of Infliximab, Ustekinumab, Adalimumab, Etanercept, and Efalizumab in the treatment of moderate to severe Ps.Based on an indirect comparison, predicted mean probability of achieving a PASI 75 of Infliximab was 80%, Ustekinumab 90 mg was 74%, Ustekinumab 45 mg was 69%, Adalimumab was 58%, Etanercept 50 mg twice weekly was 52%, Etanercept 25 mg twice weekly was 39%, Efalizumab was 26%, and placebo was 4% [52]. Biologics are used for long-term treatment because there is no evidence of cumulative toxicity or drug–drug interactions. TNF-α inhibitors are generally used after phototherapy and when conventional systemic therapies have either failed, not tolerated, or contraindicated. This second-line use is in part because of the high direct costs for drugs, which are approximately in the order of ten-times higher than the conventional systemic drugs [53]. There is a small increased risk of overall infection with the short-term use of TNF antagonists for Ps that may be attributable to differences in follow-up time between treatment and placebo groups. There was no evidence of an increased risk of serious infections and a statistically significant increased risk in cancer was not observed with the short-term use of TNF inhibitors.

Table 3: Dosage and monitoring requirement of approved biological treatments. Modified from 82.

Biologic	Dosage	Monitoring requirement
Adalimumab	80 mg SC injection day 0, 40 mg SC injection day 7 then 40 mg SC injection every 14 d.	Baseline tests: CBC (repeat at 2-3 mo then every 6-12 mo). CMP (repeat at 2-3 mo then every 6-12 mo). PPD or Quantiferon gold (repeat yearly) Hepatitis B surface antigen and core IGM antibody (repeat yearly) HCV antibody HIV and ANA
Etanercept	50mg SC injection twice weekly for 3 mo; 50 mg weekly SC injection thereafter.	
Infliximab	3-5 mg/kg per infusion at weeks 0, 2, and 6, then every 8 wk.	
Ustekinumab	45 mg (<100kg) or 90 mg (>100 kg) by SC injection at weeks 0 and 4, then every 12 wk thereafter.	
Secukinumab	150 mg or 300 mg SC injection weekly for 5 consecutive weeks followed by SC injection once every 4 wk	
Apremilast	Day 1: 10 mg o. morning Day 2: 10 mg o. morning/10 mg o.evening Day 3: 10 mg o. morning/20 mg o. evening Day 4: 20 mg o. morning/20 mg o. evening Day 5: 20 mg o. morning/30 mg o. evening Day 6 and thereafter: 30 mg o. twice daily	

Abbreviations: ANA: Antinuclear Antibody; **CBC:** Completed Blood Count; **CMP:** Comprehensive Metabolic Panel; **HBc:** Hepatitis Core Antibody; **HBsAg:** Hepatitis B Surface Antigen; **SC:** Subcutaneous; **mo**: Month; **wk**: Week; **o:** Oral.

ANTI-TNF-α

Anti-TNF-α agents are currently considered as first line biological therapies for the treatment of moderate to severe psoriasis [54]. There is no evidence of an increased risk of serious infection and a statistically significant increased risk in cancer was not observed with short-term use of TNF inhibitors [55].

Etanercept

Etanercept was the first TNF-α inhibitor to be approved for use in Ps. It is a dimeric, soluble fusion protein consisting of the extracellular ligand binding portion of the TNF receptor linked to the Fc portion of human IgG1. In 2004, Etanercept was approved by the United States Food and Drug Administration **(FDA)** for the treatment of adult Ps patients [56]. The recommended regimen for etanercept for patients with Ps is 50 mg subcutaneous twice weekly for 3 months, followed by a maintenance dose of 50 mg weekly [54]. Response rates were similar between the two low-dose regimens (50 mg per week and 25 mg per week 30% [57,58]. Patients receiving etanercept were less likely to be withdrawn in four trials [59,60] and were as likely to be withdrawn in three trials compared with placebo [61]. The long term safety profile of etanercept has been examined in patients with moderate to severe plaque Ps for up to 4 years in a series of connected trials, reviews of the literature, and a registry of patients. The most commonly reported noninfectious AEs were headache, arthralgia, injection site hemorrhage, and back pain. The most commonly reported infectious Adverse Effects **(AEs)** were upper respiratory tract infection, nasopharyngitis, sinusitis, and influenza. Data analysis with respect to malignancies showed a slight increased risk for the development of squamous cell carcinoma [62].

Infliximab

Infliximab is a chimeric (75% human and 25% murine) monoclonal antibody that acts neutralizing soluble TNF-α and blocking the membrane bound TNF-α [63]. This TNF-α inhibitor is administered by intravenous (IV) infusion. Infliximab is indicated for the treatment of psoriasis in a weight-based dosing regimen of 5 mg/kg at weeks 0, 2 and 6, then every 8 weeks [64]. PASI 75 response was achieved by 56.8% and 66.3% of patients at weeks 50 and 98, respectively [65].

The studies suggest that while infliximab can be a well-tolerated treatment for patients with moderate-to-severe plaque-type psoriasis, intermittent therapy should be avoided due to the higher incidence of serious infusion-related reactions and severe infections in this group [64,66].

Adalimumab

Adalimumab is the first fully developed human Anti-Tumor Necrosis Factor **(TNF)** monoclonal antibody approved in the US and European countries for the treatment of psoriasis. The recommended regimen is a loading dose of 80mg Adalimumab subcutaneously and then 40mg every 2 weeks starting one week after the loading dose [67]. A high proportion of patients on 40 mg adalimumab every other week achieved an improvement on the PASI 75 [67-69]. Treatment

with adalimumab was effective in patients whose disease has been refractory to systemic conventional therapies or other biologic agents [70]. Adalimumab is generally well tolerated in patients with plaque psoriasis. However, there appears to be an increased risk of Non-Melanoma Skin Cancer **(NMSC)** requiring appropriate evaluation for these patients, and the rates for total adverse events, infectious, and severe infectious events are higher in the adalimumab studies compared to the other biologic agents [71].

ANTI-IL-12/23

Ustekinumab

In 2009, Ustekinumab, a fully human monoclonal antibody that binds p40 subunit of IL-12 and IL-23 was approved for the treatment of moderate-to-severe psoriasis. Ustekinumab is administered based on weight at 45 mg (≤100 kg) or 90 mg (>100 kg) by SC injection at weeks 0 and 4, and then every 12 weeks thereafter [72,73]. PASI 75 response rates (45 mg: 61.2%; 90mg: 72.4%) at week 76 were maintained through 3 years [74,75].

The performed studies suggest that Ustekinumab is generally a safe treatment for patients with moderate-to-severe plaque-type psoriasis for up to five years. Available data suggest that long-term safety outcomes are unaffected by the dose of Ustekinumab or the cumulative exposure to the drug [71,75]. A higher incidence of NMSC was observed among patients with prior psoralen Plus Ultraviolet A **(PUVA)** exposure. The observed rate of malignancies other than no melanoma skin cancer was comparable with that expected in the general US population [75].

ANTI-IL-17A

Secukinumab

In January 2015, the FDA approved the indication of Secukinumab for the treatment of moderate to severe plaque psoriasis in adults. This drug is a recombinant, high-affinity, fully human IgG1κ monoclonal antibody that selectively binds to IL-17A and neutralizes the bioactivity of this cytokine. Secukinumab has demonstrated efficacy in treating moderate to severe plaque psoriasis in phase 2 and phase 3 studies, at the dosages of 300 mg or 150 mg for subcutaneous injection [76-80]. The proportion of patients who met the criterion for PASI 75 at week 12 is 81.6% with 300 mg and 71.6% with 150 mg of Secukinumab [81].

The physiologic impact of long-term IL-17 antagonism needs to be shown in larger and longer clinical trials. To date, the safety profile for Secukinumab is acceptable. Nasopharyngitis is the most common adverse effect. Serious infection rates were not significantly different between those treated with secukinumab compared with placebo [82].

Phosphodiesterase 4 Inhibitors

Apremilast

In September 2014, the FDA approved the apremilast for Ps treatment. The precise blockade of Phosphodiesterase 4 **(PDE4)** inhibitor, apremilast, has been shown to block the production of Interferon **(IFN)**-gamma, TNF-alpha, IL-12 and IL-23 – the pro-inflammatory cytokines that play a major role in the pathogenesis of psoriasis [83]. To date Apremilast has been evaluated in a number of clinical trials demonstrating efficacy in psoriasis [84,85]. PASI 75 response was achieved by 33.1% of patients at week 16 [84].

Anti-Drug Antibodies **(ADAs)** against biological agents may be clinically significant and potentially alter the biological drug treatment efficacy. Antibodies against infliximab, etanercept, adalimumab and ustekinumab were reported in 5.4–43.6%, 0–18.3%, 6–45% and 3.8–6% of patients. Anti-Infliximab, anti-Adalimumab and anti-Ustekinumab antibodies were associated with lower PASI responses. Although the use of concomitant methotrexate with biological agents to prevent ADAs formation in other immune-mediated diseases is promising, their use in Ps is sparse. ADAs development remains a challenge with biological therapies and therefore should be considered in patients with psoriasis who experience diminished treatment response [86].

Many new biological agents are in various phases of clinical trials (Table 3). But these drugs have their own limitations like the high cost, potential serious side-effects, indications in selected individuals, and more importantly, the lack of long-term safety data [38].

TREATMENT OF PSORIASIS DURING PREGNANCY AND BREASTFEEDING.

Topical treatments are the first line treatment of psoriasis in pregnant and lactating women. In moderate to severe cases, UVB phototherapy is the second line of treatment and the third line features, is reserved to systemic drugs.

Information found in the literature on the use of biological drugs during pregnancy and lactation is scarce, and as directed by the prescribing information packets, the use of these drugs should be avoided during pre-conception, pregnancy and lactation periods [87].

However, with respect to anti TNF-α, based on the evidence described and inferring on the currently existing guidelines on its use in patients with inflammatory bowel disease, it would be possible to adopt the following recommendations: Pre-conception exposure: since anti TNF-α hypothetically does not cross the placental barrier in the first trimester, it would be possible to allow its use until the moment of conception [88].

Exposure during pregnancy: anti TNF-α drug should be suspended during pregnancy. In case of very severe disease activity and after discussing it with the patient, it is possible to contemplate the eventual prescription or reintroduction of the drug, preferably, if feasible, with reduced doses,

larger periods between applications, and treatment suspension between 8 to 10 weeks before the expected date of delivery.

Exposure during lactation: anti TNF-α drug should be avoided during the lactation. However, in case of intense disease activity, prescribing such drugs would be possible if the benefit to the mother outweighed the risk to the child [89].

CONCLUSION

Treatment of psoriasis is still evolving. MTX, CSA and Etretinate are well-established and time-tested drugs. In recent years, there has been a vast expansion in the armamentarium of therapeutic agents for psoriasis as we have entered the exciting new era of biologic therapy. Long-term experience with biologics is still limited, both with regard to their efficacy and, more importantly, safety. Although preliminary results are encouraging, these drugs are not curative, need parenteral administration, have significant adverse effects, and additionally, loss of efficacy on long-term therapy as well as disease unresponsiveness has been observed. Therefore, the search for safer, orally administered newer and cheaper drugs is imperative.

In patients with Ps, there were limited data directly comparing systemic biologic agents with either systemic non-biologic agents or with phototherapy on an individual drug level. Overall there is insufficient evidence to determine the comparative effectiveness of individual therapies, as compared with each other between the specified classes, with few exceptions. For the comparisons of Adalimumab versus Methotrexate, Infliximab versus Methotrexate, Ustekinumab versus Methotrexate, and Etanercept versus Acitretin, there is predominantly low strength of evidence favoring the individual biologic agent versus the non-biologic treatment. Additional trials directly comparing biologic systemic agents, systemic non-biologic agents, and phototherapy are needed [90]. We need to have more studies that provide the cost efficacy data that may influence Ps treatment selection.

Table 4: New systemic therapies for Psoriasis. Modified from [100].

Drug	Current status	Mechanism of action
Ixekizumab	Phase 3 trials underway	Anti-IL 17
Brodalumab	Phase 3 trials underway	Anti-IL 17
Tildrakizumab	Phase 3 trials underway	Anti-IL 17
Guselkumab	Phase 3 trials underway	Anti-IL 17
Tofacitinib	Phase 3 trials complete	Janus Kinase inhibitor
Ruxolitinib	Phase 2 results available	Janus Kinase inhibitor

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