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PSORIASIS (JAISHIN WU, SECTION EDITOR)

Update on Oral Therapy for Psoriasis

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Abstract
Purpose of Review The aim of this review article is to summarize the information of oral treatments of psoriasis, with emphasis in new information and newer drugs.
Recent Findings Methotrexate has an adequate efficacy and safety profile with low cost and large real-life evidence. Cyclosporine's therapeutic power is abated by the long-term safety issues. Acitretin has a niche in special circumstances such as combination with phototherapy, HIV population, or special forms of psoriasis such as palmoplantar, pustular, and erythrodermic psoriasis. Apremilast, the newer available drug of this group demonstrates a modest but acceptable efficacy and good safety in this population. Other drugs have been evaluated with different results in this field.
Summary Oral therapy for psoriasis is widely used in patients with moderate to severe disease; thus, it is crucial to know the latest information and indications as well as the recent development of new drugs.

Keywords Methotrexate · Cyclosporine · Acitretin · Apremilast · Psoriasis

Introduction

Even when most of the clinical trials are focused on biologics agents, oral therapy in psoriasis is still the most widely used for patients with moderate to severe disease worldwide due to its price, experience, and efficacy. The oral therapy agents (and topical therapy ones) belong to the group of small molecules. Small molecules are low-molecular-weight inhibitors (< 1 kDa) that are able to modulate pro-inflammatory cytokines [1] or cytokine receptors, blocking intracellular targets such as transcriptional factors or enzymes [2]. Due to their size, they can be administered either orally or topically [2] and their production is less expensive than that of a biologic [2]. Small molecules represent a more cost-effective option than biological therapies for the treatment of psoriasis [1, 3, 4]. Classical immunosuppressant oral therapy such as methotrexate and cyclosporine as well as the recently approved apremilast belongs to this group. Acitretin, an oral, non-immunosuppressive medication that also belongs to this group, will be discussed.

This article is part of the Topical Collection on *Psoriasis*

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Methotrexate

Methotrexate has been used for moderate to severe psoriasis for over half a century. Methotrexate has antiproliferative and immunomodulatory effects [5••, 6]. New evidence has been published regarding its effectiveness, safety, and drug survival. A 2016 meta-analysis [7••] estimated that 45.2% of patients achieved a PASI75 by 12–16 weeks ($n = 705$) and reported treatment-limiting adverse events in 6.9% of patients treated for 6 months ($n = 2763$), presenting an acceptable level of safety (Table 1).

In relation to subcutaneous methotrexate therapy, a 2016 randomized controlled phase 3 trial [18] assessed the effect of an intensified schedule in patients with PASI score ≥ 10. Patients were assigned to a dose of 17.5 mg/week ($n = 91$) or placebo ($n = 29$). If patients did not achieve at least PASI50 after 8 weeks, the dose was increased to 22.5 mg/week (31%). Forty-one percent of patients achieved a PASI75 at 16 weeks in the methotrexate group and 10% in the placebo group. PASI75 at week 52 was achieved in 45% of patients in the methotrexate group. Methotrexate was well

Table 1 Summary of safety and efficacy data of available oral treatment for psoriasis

Oral agent	Dosage	PASI75	Time for achieving PASI75	Monitoring	Main contraindications	Special considerations
Methotrexate	7,5–25 mg/week	45.2% [7••]	Weeks 12–16 [7••]	Blood count and liver and renal function.	Pregnancy Liver or renal impairment Respiratory impairment	Avoid excessive alcohol Subcutaneous administration: decrease gastrointestinal intolerance Folic acid supplementation is required
Cyclosporine	2,5–5 mg/kg/day	50–71% [8–11]	Weeks 12–16 [8–11]	Blood pressure, creatinine, serum urea nitrogen, blood count, serum magnesium, potassium, liver function	Uncontrolled or severe hypertension Serious infection Immunocompromised Abnormal renal function	Pregnancy: class C Useful in psoriatic crisis and unresponsive to other modalities Duration limited to 1–2 years or less
Acitretin	10–50 mg/day	34–52% [12–14]	Up to 6 months [15]	Liver function Lipid panel	Pregnancy Severe renal or hepatic impairment Elevated lipid levels Blood donation during tx and for > 3 years after treatment	Pregnancy contraindicated during tx and for >3 years after treatment Avoid alcohol in female patients
Apremilast	30 mg PO Bid	28.8–33.1% [16•, 17]	Week 16 [16•, 17]	Not required	Not described	Nausea, diarrhea, and weight loss are described

tolerated without serious adverse events. Only 3% presented digestive intolerance, a reason for which treatment was discontinued. Compared with other studies with oral methotrexate [19, 20], subcutaneous methotrexate presented a faster and more prolonged clinical response at 8 and 52 weeks, respectively.

Methotrexate is used as a therapeutic option for long-term treatment, but data on its long-term use is scarce. A 2017 study extracted from a prospective psoriasis registry (MTX-CAPTURE) [21•] describes 5-year drug survival for methotrexate. Eighty-five patients were included, with a median survival of 1.8 years and a maximum treatment duration of 5.2 years. The overall drug survival rates were 62% after 1 year, 30% after 3 years, and 15% after 5 years. Sixty-four percent of patients discontinued methotrexate ($n = 55$). The drug survival rate due to side effects was 76% after 1 year, 50% after 3 years, and 25% after 5 years. The drug survival rate due to ineffectiveness was 83% after 1 year, 59% after 3 years, and 59% after 5 years. The main causes of discontinuation of methotrexate were side effects in 34% ($n = 19$), ineffectiveness in 25% ($n = 14$), and both in 12% ($n = 7$) of cases. The most commonly reported side effect for discontinuation was gastrointestinal symptoms. A high PASI and Visual Analogue Scale for disease severity at baseline were determinants for a short survival time.

Another important study published in 2016 [22] evaluated the discontinuation of methotrexate treatment in psoriasis patients under real-world conditions ($n = 333$ patients). The largest proportion of treatment failures occurred during the first year of treatment (32%), mainly in the first 3 months, and continued to drop up to 9 months. In the first year, the rate of treatment discontinuation due to adverse effects was 24% and to lack of efficacy was less than 10%. The lack of efficacy as a limiting factor was less prevalent than commonly assumed. The main reason to stop methotrexate was adverse events. Beyond the first year of use, patients are likely to remain on the treatment, reducing the use of other treatment with topical agents or phototherapy.

Methotrexate has an acceptable clinical efficacy with a good safety profile and with a relatively low cost (Table 1). Subcutaneous administration appears to have advantages over oral administration, although quality clinical studies are still lacking.

Cyclosporine

Cyclosporine is an immunosuppressive therapy that interferes with T cell activation. New evidence has been published regarding the effectiveness of low-dose cyclosporine and associated adverse events. A 2017 brief report in 67 patients with psoriasis vulgaris evaluated the immunosuppressive effect of low-dose cyclosporine [23•]. Thirty-nine patients were treated with cyclosporine 100–200 mg/day with a mean duration of

19 months. Venous blood samples were collected and analyzed in a flow cytometer for CD3, CD4, CD8, CD19, and CD16/56 cell surface markers. In the treatment group, the PASI score decreased significantly from baseline. There were no differences in the number of T, B, or NK cells in both groups, suggesting that low-dose cyclosporine treatment should be an immunomodulatory therapy and not an immunosuppressive treatment.

The GENDER ATTENTION observational study [24] investigated the influence of gender and menopause on the incidence of adverse events during cyclosporine treatment (3 mg/kg) in psoriatic patients. This multicenter prospective study enrolled 969 adult psoriatic patients. Thirty-four percent of patients reported at least one adverse effect. There was a higher incidence of adverse effects in postmenopausal women (42.3%) compared with fertile women (31.3%), but there were no differences in fertile or postmenopausal women compared to age-matched men. Postmenopausal women had fewer grade 1–2 adverse events but more grade 3–4 adverse events compared to fertile women. This is the first study that analyzed the sex incidence of adverse effects during psoriasis cyclosporine treatment in real life.

In relation to adverse events during cyclosporine treatment of psoriatic patients, the Spanish registry of systemic therapy in psoriasis (BIOBADADERM) [25•] evaluated drug survival for classic and biological systemic drugs. The main causes of cyclosporine discontinuation ($n = 329$) were remission (33.1%), lack of efficacy (26.1%), and adverse events (17.6%). The drug survival probability at the first year for all causes was 23.3%; for lack of efficacy it was 67.8%, for adverse events 78.5%, and for remission 60.3%. In another study with the same Spanish Biologics Registry [26•], cyclosporine had the highest incidence rate of adverse effects leading to drug discontinuation among biologics and traditional systemic therapies, with 49 events/100 patient years, with a median of time of 3 months. The main causes for drug discontinuation were gastrointestinal disorders, infections and infestations, and hepatobiliary disorders (Table 1). In another study, the risk of hypertension associated with cyclosporine in psoriasis patients [27] was estimated at an odds ratio of 7.13 (95% confidence interval 1.85–27.49) compared to patients not exposed to this drug.

Acitretin

Acitretin is a synthetic aromatic retinoid that influences the transcription of over 500 genes, many of which are involved in keratinocyte proliferation and differentiation, and the migration of neutrophils [28, 29]. Therefore, it has been traditionally used in the treatment of severe psoriasis, pustular and erythrodermic psoriasis, and other keratinization disorders such as palmoplantar keratoderma, pityriasis rubra pilaris, and lamellar ichthyosis. Unlike other systemic therapies for psoriasis, acitretin does not result in immunosuppression, which makes it especially suited for the HIV-positive population.

Clinical experience suggests acitretin to be best suited for long-term maintenance therapy, as there is no significant decline in efficacy over time [30].

When acitretin was first introduced around 30 years ago, clinical trials were conducted in order to compare acitretin with its preceding retinoid (etretinate); they found the two drugs to deliver similar efficacy [12]. Similarly to methotrexate, the effect of treatment in chronic plaque-type psoriasis is usually noticeable after 2 or 3 months, with a peak effect at 6 months [15]. Overall, actiretin has been shown to achieve a PASI50 response in 66–85% of patients and a PASI75 response in 34–52%, but efficacy is dose-dependent [12–14].

Due to these modest results, acitretin has been usually favored, both in long-term clinical experience and clinical trials, as a combined therapy (with UV radiation and/or topical therapy), in which case the effectiveness is similar to other classical psoriasis therapies. In a placebo-controlled study, the addition of calcipotriol to acitretin led to a PASI reduction of 74% (versus 51% in the placebo group) and to a lowering of total acitretin dose to reach clearance [31]. The combination of acitretin and photochemotherapy increases the efficacy of light therapies and has a retinoid dosage-sparing effect, which can reduce side effects [32] and help prevent erythema, as acitretin thins the stratum corneum in a dose-dependent manner. In a double-blind comparative study that evaluated phototherapy without or in combination with acitretin, marked or complete clearing occurred in 80% of patients without acitretin and in 96% of the patients on the combined arm [33]. In addition, the combination has a lowering effect on the amount of light exposure time needed to achieve clearing (15 h in combination with broadband UVB versus 21 h in UVB monotherapy) [34].

Acitretin is a convincing therapeutic option in some particular forms of psoriasis, such as palmoplantar pustulosis (PPP), generalized pustular psoriasis (GPP), erythrodermic psoriasis, and HIV (acitretin has no immunosuppressive role). Two RCTs have compared acitretin with placebo in PPP, both of which showed a five- to tenfold reduction in pustules in a period of 4 weeks [35, 36]. In a large uncontrolled study that compared the effectiveness of acitretin, methotrexate (MTX), cyclosporine (CsA), and PUVA in GPP, acitretin was shown to be superior to the other modalities (84% with acitretin versus 76, 71, and 46%, respectively) [37].

Apremilast

Apremilast was the first "new" small molecule to receive FDA approval for the treatment of psoriasis. Apremilast inhibits the activity of cyclic AMP phosphodiesterase-4 (PDE-4), an intracellular enzyme expressed in immune cells that hydrolyses

cAMP into AMP, which leads to the production of pro-inflammatory cytokines involved in psoriasis, such as TNFa, IL12, IL23, IL17, and IL22, as well as the suppression of anti-inflammatory cytokines [38]. The safety and efficacy of apremilast in plaque psoriasis were assessed in the ESTEEM-1 [16•] and ESTEEM-2 [17] phase III multicenter clinical trials. Safety data in these trials and others have shown that the most frequent side effects of apremilast were diarrhea, vomiting, nausea, headache, and upper respiratory infections. Most cases of diarrhea and nausea were noted to be dose-dependent and resolved within 4 weeks despite continuous treatment. Serious adverse effects were similar to placebo. Weight loss seems to be reported frequently (19.2% reported a weight reduction of over 5%), but it occurs only during treatment and has not been reported to be severe or to be associated with the presence of vomiting or diarrhea [39].

Interestingly, abnormal laboratory results were also similar to placebo, which suggest that apremilast could be indicated without monitoring laboratory tests [16•].

Unlike MTX and CsA, apremilast does not need dose adjustment in hepatic insufficiency, but the dosage should be scaled down in renal failure [40]. When contrasted with TNFa inhibitors, apremilast has not shown TB reactivation or worsening of heart failure.

In terms of efficacy, apremilast reached a PASI75 response in around 30% of patients at week 16 (versus 5.8% in the placebo arm) (Table 1). Strikingly, patients with scalp, palmoplantar, and nail psoriasis all exhibited convincing results. The scalp physician global assessment improved with apremilast, from 3 or more (moderate to severe) to 0–1 (clear or minimal) in 40.9 versus 17.2% in placebo. Palmoplantar psoriasis improved in 65.4% of cases on apremilast, compared to 31.3% on placebo, and the nail psoriasis severity index was reduced in 44.6% of patients compared to 18.7% in the placebo group. All of the above were statistically significant [17].

Other Therapies Under Investigation

A growing number of small molecules are being evaluated for the treatment of psoriasis nowadays, including JAK inhibitors and A3 adenosine receptor agonists (AARs) [41].

The JAK protein tyrosine kinase (PTK) family is made up of cytoplasmic PTKs that play an essential role in cytokine signal transduction pathways, through their association with various cytokine receptors involved in the pathogenesis of psoriasis [41]. Tofacitinib is an inhibitor of JAK1 and JAK3 signaling. It has been approved by FDA to treat rheumatoid arthritis (RA; 5 mg twice daily) since 2012 [42], with several trials showing its safety and efficacy [43, 44]. Several data on psoriasis are also available [45, 46•]. A phase III, randomized, double-dummy, placebo-controlled, 12-week study tested non-inferiority of tofacitinib 5 and 10 mg BID, compared with high-dose etanercept or placebo [46•]. Ten milligrams BID was non-inferior to etanercept 50 mg twice weekly in both coprimary end points PASI75 and PGA. The adverse event (AE) rates over 12 weeks were similar for tofacitinib and etanercept [46•]. A long-term efficacy and safety study of up to 54 months in an open-label extension was published recently. It demonstrated that the safety profile was stable for up to 66 months of tofacitinib treatment, and the adverse event rate was consistent with that observed in the phase 3 studies; no new safety risks were observed. The efficacy achieved during the randomized clinical trials was sustained through month 54 in this long-term extension [47].

Tofacitinib has showed an increased risk of infection and malignancy. Pooled data from 1-year-long phase II and III clinical trials, and a long-term extension trial, of patients who have received tofacitinib for psoriasis ($n = 3623$) indicate that incidence rates for serious infections, herpes zoster, and non-melanoma skin cancers were numerically though not significantly higher with the higher dose (10 versus 5 mg twice daily) [48]. Data from the RA studies of tofacitinib suggest "significant immunosuppression," according to the FDA, as the document also establishes, "increasing exposure to tofacitinib increases the risk of malignancy" [49]. The FDA denied approval for its use in the treatment of psoriasis in 2015, because the higher dose (10 mg) of tofacitinib gave rise to safety concerns and was not considered to have an adequate risk-to-benefit ratio [41, 50].

Tofacitinib has also been tested as a topical treatment for psoriasis. In a vehicle-controlled phase IIa trial studying a topical tofacitinib 2% ointment formulation BID, Ports et al. reported an improvement in the target plaque severity score at week 4 [51].

Another JAK inhibitor is ruxolitinib that preferentially inhibits JAK1 and JAK2. It is approved for the treatment of polycythemia vera and myelofibrosis. This drug was first investigated as a topical formulation (INCB018424, Incyte) for use in psoriasis [52]. In a phase IIa trial comparing topical INCB018424 0.5, 1, and 1.5% cream in a double-blind, vehicle-controlled trial, it was shown to be safe and effective with improvement in total lesion score, PGA, and PASI [53].

There are additional JAK inhibitors undergoing investigation for the treatment of moderate to severe psoriasis [54], such as baricitinib (INCB-28050/LY3009104), a JAK1 and JAK2 inhibitor, that is being examined. In a phase II, dose-ranging, randomized, double-blind study, 238 patients with moderate to severe psoriasis were assessed to evaluate the safety and efficacy of baricitinib. Patients were randomized to receive placebo or baricitinib in 2, 4, 8, or 10 mg (qd) doses throughout 12 weeks. At week 12, patients were submitted to dose adjustments for an additional 12 weeks of treatment, based on PASI improvement responders. After 12 weeks of treatment, 43% of patients in the baricitinib 8 mg group and 54% of patients receiving baricitinib 10 mg achieved PASI75 compared with 17% of patients on placebo. At week 24, most

responders (82%) maintained their PASI75 score, while 43% of partial responders and non responders, receiving the same or higher doses, achieved PASI75. The type and incidence of adverse events were similar throughout the study [3, 55, 56].

Peficitinib ASP015K is an orally active JAK3 inhibitor. A phase 2a multicenter, double-blind, randomized, placebo-controlled study showed dose-dependent improvements in clinical and histological measures of severity over 6 weeks of treatment. At all doses, ASP015K was well tolerated, with no reported serious adverse events [57].

AArs are G protein-coupled receptors that are involved in a variety of intracellular signaling pathways and physiological functions. AAr activation with a specific agonist (CF101) downregulates the nuclear factor-κB signaling pathway, inhibits the proliferation of specific autoreactive T lymphocytes, and induces apoptosis of inflammatory cells [41, 58]. These effects result in the downregulation of pro-inflammatory cytokines, such as TNFα, IL-6, and IL-12 [59]. In a phase II, multicenter, dose-ranging study, patients with moderate to severe plaque-type psoriasis were treated with CF101 at different doses, or placebo, administered orally BID for 12 weeks. In the 2-mg CF101-treated group, a significant improvement in PASI was observed at weeks 8 and 12. In this group, 35.3% of the patients achieved a PASI50 response. Side effects reported were considered mild [60].

Other options under early investigations are PKC inhibitors such as sotrastaurin (AEB071), MAPK inhibitors such as BMS-582949, SYK inhibitors, sphingosine 1-phosphate receptor agonists (ponesimod), and the A3AR agonist CF101 [2].

Conclusion

When dealing with a patient with moderate to severe psoriasis, oral therapy is still the most used agent in the world. Therefore, a physician must have updated information and extensive knowledge in its use, action, and adverse effects. Many of these drugs have been used for years; therefore, they have few or no recent studies and their effects are known based in real-life use. This lack of data limits their comparisons in an evidence-based medicine. However, these therapeutic tools are useful and should be offered to patients in the range of possibilities that we nowadays have for the treatment of psoriasis. New oral treatments are available and others are being researched to enrich the therapeutic arsenal in this pathology, which still needs new drugs to improve the effectiveness and safety of interventions and improve the quality of life of our patients.

Compliance with Ethical Standards

Conflict of Interest Dr. Fernando Valenzuela declares consultancy for Pfizer, Novartis, and Janssen; expert testimony for Novartis, AbbVie, and Deutschepharma; and payment for development of educational presentations including service on sopeakers' bureaus for Novartis, AbbVie, and Deutschepharma.

Drs. Javier Fernández and Pablo Santa María declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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•• Of major importance

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