CLINICAL MANAGEMENT RECOMMENDATIONS

Psoriasis Therapy Beyond Biologics

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ABSTRACT

Although psoriasis patients have benefited from the advent of biologic treatments over the past two decades, these medications are not appropriate for all patients and can be augmented by additional therapy. Differences among the manifold options can be difficult to parse, though essential for matching treatment with an individual patient. UV-light therapies, including both UV-B and psoralen with UV-A light, continue to play an important role in treatment, as do non-biologic systemic options including methotrexate, cyclosporine, apremilast, and acitretin. Recent years have seen a dramatic expansion in available topical therapies, the most common modality for the treatment of psoriasis, including new foam, spray, lotion, and cream formulations of topical corticosteroids (TCS) and new fixed-dose combination offerings of TCS with tazarotene and calcipotriene. Newer advances, including the oral tyrosine kinase 2 inhibitor deucravacitinib and non-steroidal topicals such as roflumilast, a PDE-4 inhibitor, and tapinarof, a first-in-class non-steroidal small-molecule, will soon provide even more options for treatment. It is vital for clinicians to remain aware of this ever-expanding armamentarium, allowing for more productive shared decision-making with patients, improved satisfaction, and better disease control.

INTRODUCTION

Psoriasis is a chronic, relapsing, immune-mediated condition that affects roughly 3% of the US population and an estimated 125 million individuals worldwide. Plaque psoriasis is the most common form of the disease, manifesting as well-demarcated scaly erythematous patches and plaques on extensor surfaces, often with intense pruritus.

The advent of biologics, including TNF inhibitors, IL-12/23 inhibitors, IL-17 inhibitors, and IL-23 inhibitors, as treatment for psoriasis has heralded an era of remarkably improved therapies, particularly for moderate to severe plaque psoriasis and psoriatic arthritis. However, these medications are not necessarily appropriate or needed for every patient.

In this review we will discuss available treatments and pearls regarding non-biologic options for psoriasis, with a brief review of non-biologic systemic therapies followed by an in-depth discussion of recent advances in topical therapeutics and recommendations as to their inclusion in patient care.

ORAL SYSTEMIC TREATMENT

As biologic systemic therapies available for the treatment of psoriasis have proliferated in recent years, traditional oral systemic

treatments [Table 1] have fallen relatively out of favor. Since the approval of apremilast in 2014, there have been no new oral agents approved for the treatment of plaque psoriasis. The side effect profiles of therapies in this category should be carefully considered before initiating therapy.

Table 1. Non-biologic systemic therapies for plaque psoriasis

Medication	Treatment success rates*	Advantages
Methotrexate	45.2% at week 12 or 16[3]	Highly effective therapy at low cost
Acitretin	47% at week 12[46]	No immune suppression
Cyclosporine	50-97% at week 10-16[47]	Excellent bridge to alternative therapy for control of severe disease
Apremilast	30-40% at week 16[11-13]	No monitoring needed
Deucravacitinib†	50.3%-53.6% at week 16[16]	Oral dosing with efficacy approaching injectable biologics

*Based on reported PASI75 over multiple studies
†Phase III trials ongoing, application for regulatory approval pending

Methotrexate

One of the oldest treatments for psoriasis available today and the most commonly prescribed for psoriatic arthritis, methotrexate, is a dihydrofolate reductase inhibitor usually dosed at 15-20 mg once weekly for psoriasis.[2] Studies have shown that patients achieve at least a 75% improvement in the Psoriasis Area and Severity Index (PASI75) at week 12 or 16 in 45.2% of patients as compared to 4.4% with placebo.[3] However, use can cause hepatic fibrosis and cirrhosis, irreversible lung injury, bone marrow suppression, renal toxicity, diarrhea and ulcerative stomatitis, birth defects, and predisposition to infections.[4] Many insurers still require a trial of methotrexate prior to initiation of biologic therapy, and its effectiveness and cost make it a fair option for most patients.

Cyclosporine

The cyclophilic peptide cyclosporine, originally approved for treatment of psoriasis in 1997, acts via calcineurin inhibition and independent dampening of T-cell activation.[5] A recent network meta-analysis found that 2.5–5 mg/kg/day for 12–16 weeks results in a PASI90 equivalent to that of Methotrexate.[6] However, potential adverse effects are also a significant barrier to treatment, including nephrotoxicity, hepatotoxicity, hypertension, paresthesia, hypertrichosis, gingival hyperplasia, electrolyte disturbances, increased risk of infections, and increased risk for skin and lymphoproliferative malignancies.[7] Cyclosporine is typically used as a bridging therapy to assist with rapid control of severe or poorly controlled psoriasis while another long-term therapy is being initiated. Long-term use of cyclosporine beyond 3 months is uncommon and use over 1 year is not recommended.

Acitretin

Acitretin is a vitamin A derivative whose mechanism of action involves binding of an intracellular receptor, leading to improved regulation of epidermal proliferation.[8] Studies of acitretin since its approval for the treatment of psoriasis in 1996 have demonstrated that doses of 25-50 mg/day prove less effective than other traditional systemic agents.[9] Acitretin use is likewise limited by side effects, including skeletal toxicity, hepatotoxicity, hyperlipidemia, mucocutaneous effects, arthralgia, myalgia,

and pseudotumor cerebri.[10] However, its lack of immunosuppressive side effects makes it a good choice for patients for whom another systemic therapy would not be appropriate. It would not be an appropriate choice in most women of child-bearing age, given teratogenic effects that persist for 2-3 years even after cessation of therapy, nor for those with concomitant PsA, on which it has no effect.[9]

Apremilast

The newest non-biologic systemic therapy for psoriasis, apremilast, is a phosphodiesterase-4 (PDE-4) inhibitor that modulates both the immune response and epithelial proliferation.[11] Studies have shown that 30-40% of patients achieve PASI75 after 16 weeks of treatment with 30 mg twice daily.[11-13] Use is limited by the most prominent side effects of diarrhea and weight loss, infections, depression, and headache, though no standard blood draws are required for routine monitoring, unlike all other oral options, making it a better choice for those who would be unable to sustain a monitoring visit schedule.[10]

Emerging oral therapies

While JAK inhibitors such as tofacitinib showed good results in clinical trials, doses needed for control of plaques proved too high, and potential safety issues too significant, to recommend their use in treatment beyond PsA.[14] Although not yet approved by the FDA, the oral tyrosine kinase 2 (TYK2) inhibitor deucravacitinib has shown great promise in recent trials. A phase II trial testing various dosing regimens noted up to 75% PASI75,[15] and phase III trials of 6 mg daily treatment are ongoing, with preliminary data showing superiority to both apremilast and placebo over 16 and 24-week treatment courses.[16]

PHOTOTHERAPY

Although use of phototherapy for the treatment of psoriasis has decreased dramatically since the advent of biologic therapy,[1] it remains an important option in the right patient setting.

UV-B

UV-B light was originally used in broadband form (290-320 nm), but is now almost exclusively used as narrowband (311 nm) light for the treatment of psoriasis, given improved clinical efficacy.[17] Treatment with UV-B light decreases DNA synthesis, inducing apoptosis of pathogenic T-cells and proliferating keratinocytes, as well as causing local and systemic immunosuppression.[18] Treatment begins at up to 3 times weekly, though can eventually be tapered to twice per week or less. Excimer laser/lamp, which uses a monochromatic UV-B source at 308 nm, can be used for highly targeted therapy of individual lesions.

PUVA

Psoralen and UV-A light (PUVA) provide a photochemotherapy in which a photosensitizing drug, psoralen, is given either systemically or topically prior to UVA (320-400 nm) radiation. Similar to UVB treatment, administrations start at 2-3 times weekly, with tapering over the longer term once disease control has been established. Although PUVA has proven more efficacious than UVB for refractory disease,[18] concerns over the long-term carcinogenic risk of UVA as well as GI distress caused by systemic psoralens tend to limit its usage in the clinic.[19]

TOPICAL THERAPIES

Eighty percent of psoriasis patients are thought to have disease amenable to topical therapy,[20] though significant issues in compliance prove to be a formidable barrier to disease control.[21] The therapeutic options in this space are constantly advancing [Table 2], driven largely by patient dissatisfaction with current options.[22] Reviewing all available topical therapies is beyond the scope of this brief article, and there are excellent reviews of topical therapies elsewhere in the literature,[23,24] so here we will review the most recent advances in the field along with recommendations as to their inclusion in clinical practice. As patient preferences for topical therapies can be heterogeneous and difficult to predict, with many valuing delivery mode more than proven efficacy,[25,26] it is imperative that the choice of topical therapy be a collaborative decision.

Steroidal formulations

Topical corticosteroids (TCS) have been the cornerstone of psoriasis therapy since the 1950s, largely offered as creams, ointments, and lotions that act through anti-inflammatory, antimitotic, immunomodulatory, apoptotic, and vasoconstrictive functions. Advances in vehicle technology have allowed for the development of sprays and foams, as well as improvements upon lotion vehicles, all of which can dramatically improve the user experience by leaving less residue and being less bothersome to apply than traditional formulations. Betamethasone dipropionate (BD) 0.05%, previously available in ointment, lotion, and cream formulations, is now available as a twice-daily spray, which outperforms vehicle alone and provides relief comparable to the corresponding superpotent lotion, while rating only mid-potency by vasoconstrictive assay, indicating a decreased risk for atrophy, HPA-suppression, and other common TCS side effects.[27,28] Halobetasol propionate (HP) 0.05%, likewise previously available in ointment, lotion, and cream formulations, is now offered as a twice-daily foam that can provide control of symptoms after a two-week course.[29] This foam also appears to show minimal systemic absorption and no HPA axis suppression in those age 12-18, though pediatric use is currently off-label.[30] HP is also now available as a 0.01% lotion, one-fifth of the traditional 0.05% concentration, that can be used daily over an extended 8-week treatment course, useful for those patients who desire a more extended therapeutic treatment without sacrificing efficacy.[31,32] Finally, clobetasol propionate (CP) is newly available as a 0.025% cream that not only halves the traditional concentration of 0.05% without the loss of super-potent (class I) status, but also avoids traditional potency enhancers that are the leading cause of TCS contact allergy, making this an excellent option for those with proven allergies to other TCS, propylene glycol, or sorbitan sesquioleate.[33]

Fixed-dose combination formulations

The combination of calcipotriene, a vitamin D analogue, and TCS has previously required either the application of two separate medications or the use of a fixed combination suspension or ointment. As of 2015 and 2020, respectively, both a foam and cream fixed-dose combination therapy of BD 0.064% and calcipotriene 0.005% (Cal/BD) are now available. Given increased

Table 2. New and Upcoming Topical Therapies for Psoriasis

Medication	Treatment success rates*	Advantages
Calcipotriene 0.005% plus betamethasone dipropionate 0.064% aerosol foam	38-54.6% after 4 weeks of daily application[48-50]	Foam vehicle; combined therapy; once-daily application
Betamethasone dipropionate spray, 0.05%	34.5% after 4 weeks of twice-daily application[51]	Spray vehicle; decreased side effects
Clobetasol propionate cream, 0.025%	30.1-30.2% after 2 weeks of twice-daily application[33]	Lower steroid concentration than traditional; elimination of allergens
Halobetasol propionate foam, 0.05%	25.3%-30.7% after 2 weeks of twice-daily application[29]	Foam vehicle
Halobetasol propionate lotion, 0.01%	37-38% after 8 weeks of daily application[31,32]	Lower steroid concentration than traditional
Halobetasol propionate 0.01% plus tazarotene 0.045% lotion	35.8%-45.3% after 8 weeks of daily application[39]	Combined therapy; extended application regimens
Calcipotriene 0.005% plus	37.4% after 8 weeks of daily	Combined therapy; new less greasy cream formulation;

betamethasone dipropionate 0.064% cream	application[52]	extended application regimens
Tapinarof 1% cream†	35.4-40.2% after 12 weeks of daily application[44,53]	Non-steroidal; extended application regimens
Roflumilast 0.3% cream†	37.5-42.4% after 8 weeks of daily application[42]	Non-steroidal; extended application regimens
Roflumilast 0.3% foam†	‡	Foam vehicle; non-steroidal; extended application regimens

*Physician's Global Assessment of clear or almost clear, with success rate based on phase III trials only
† Phase III trials ongoing, application for regulatory approval pending
‡ Phase III trial data not yet released
Adapted from Buechler et al, 2021[54]

bioavailability and enhanced penetration with the foam formulation,[34] Cal/BD foam provides greater treatment efficacy than Cal foam, BD foam, Cal/BD gel, and Cal/BD ointment.[35] A crossover trial showed that half of patients studied strongly preferred Cal/BD foam to Cal/BD gel as well as their latest topical treatment, particularly if that topical treatment had been an ointment or cream.[26] Cal/BD cream, meanwhile, relies on a proprietary cream with decreased surfactant and thus improved medication delivery with decreased irritation, and it has outperformed topical suspension in trials.[36,37]

Tazarotene, a vitamin A derivative, can also be used alongside topical steroids to increase efficacy and alleviate safety concerns, although it does carry an independent risk of teratogenicity, photosensitivity, and irritation.[38] A fixed-dose lotion of HP 0.01% plus tazarotene 0.045% (HP/Taz) approved in 2019 can be used as topical monotherapy for courses of 8 weeks, with greater treatment success than either therapy alone and sustained treatment effect over the ensuing 4 weeks.[39] If this extended course of therapy is insufficient, recent data suggest HP/Taz lotion can be used daily for up to a year in repeated 4-week intervals on an as-needed basis without adverse events or local skin changes.[40]

Emerging non-steroidal topicals

While shortened courses and combination therapy help decrease the risk of TCS side effects, such issues continue to be a long-term concern for many patients, and as such non-corticosteroid topicals have long been a focus of drug development. Existing non-steroidal topical therapies include tazarotene and calcipotriene, as mentioned above, as well as calcineurin inhibitors, coal tar, and keratolytics such as salicylic acid. These therapies can be particularly useful for pediatric applications, intertriginous and sensitive locations, and long-term therapy. However, the stronger anti-inflammatory and antiproliferative effects as well as the ease-of-use of TCS has led to the marginalization of these therapies in the clinic. This therapeutic category stands to make a marked resurgence in the coming years with new PDE-4 inhibitor and small-molecule topical therapies soon to seek FDA approval. Both of these novel therapies offer promising efficacy, good local tolerability and the potential for a durable remission. Roflumilast, a PDE-4 inhibitor, may soon be available in both cream and foam vehicles.[41] Clinical trials of Roflumilast cream show rates of treatment success comparable to available topical treatments with a safety profile that has allowed enrollees as young as two years of age.[42] Though farther away from regulatory approval, Roflumilast foam has shown similar promise, and would pair the safety profile of the PDE-4 inhibitor with the popular and easy-to-use foam vehicle.[43] Tapinarof, a novel, first-in-class, non-steroidal small-molecule, has shown treatment efficacy at 12 weeks that is similar to that of other topicals,[44] as well as further efficacy from continued daily use for up to a year without evidence of tachyphylaxis or any new adverse effects.[45]

CONCLUSION

While the advent of biologic therapies has shifted treatment strategy, non-biologic options remain essential for psoriasis care at all stages of severity. Currently available and emerging oral, topical, and UV-light based therapies can achieve excellent disease control, in addition to being adjuncts to biologic therapy when appropriate. Upcoming advances in therapy with new oral TYK2 inhibitors and non-steroidal

topical options will dramatically affect the future treatment paradigm. It is imperative for dermatologists to remain informed about this changing landscape, as shared decision-making with patients regarding desired characteristics, unwanted side-effects, and level of expected efficacy of treatment modalities can lead to improved satisfaction and disease control.

Conflict of Interest Disclosures: Dr. Buechler and Dr. Veenstra have nothing to disclose. Dr. Stein Gold reports grants and personal fees from Leo Pharma, Arcutis, Abbvie, UCB, BMS, Amgen, Incyte, Ortho Derm, Pfizer, Dermavant, and Sun.

Funding: None

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