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Topical Therapy for the Management of Childhood Psoriasis: Part I

K. M. Cordoro, MD

Department of Dermatology, University of California, San Francisco, CA, USA

ABSTRACT

Psoriasis represents a potentially life-altering disease that can profoundly impact physical, emotional and social functioning, and overall quality of life. The majority of cases are mild and managed adequately with topical medications. A minor subset of children present with severe, rapidly evolving disease that requires systemic therapy. The choice of treatment in children, as in adults, is determined by disease acuity, morphology, distribution, severity and the presence of comorbidities such as psoriatic arthropathy. Practical considerations such as ease of use, patient acceptability, accessibility, risk to benefit ratio, cost and individual perceptions of disease and quality of life are factored into treatment decisions. Part I of this 2-part series will focus on topical agents, their varying degrees of effectiveness, potential side-effects and applications in clinical practice.

Keywords: anthralin, calcineurin inhibitors, calcipotriene/ calcipotriol, children, coal tar, corticosteroids, psoriasis, salicylic acid

Topical Therapy

Monotherapy may be effective for limited, focal or mild disease. In cases where multiple medications are necessary, the number of agents that must be applied can be reduced by compounding compatible agents. Research the surrounding community and keep a list of compounding pharmacies to provide to your patients. Ointment formulations tend to have greater efficacy than creams but some patients, particularly adolescents, find them objectionable. In an effort to increase compliance, prescribe whichever vehicle the patient finds preferable.[1] Thick, greasy ointments can be used at nighttime and more cosmetically acceptable creams, lotions and solutions reserved for daytime use.

Corticosteroids

Corticosteroids remain among the first line agents in the topical treatment of psoriasis in all age groups. Delivering the steroid to the involved skin in a convenient, tolerable, safe and efficacious manner requires selection of a vehicle that is well-suited to site-specific qualities such as hair (scalp), moisture (intertriginous zones) and occlusion (axillae, diaper area, gluteal cleft). A variety of vehicles are available to choose from and include powders, sprays, lotions, solutions, creams, emollient creams, ointments, gels, tape and foam.[2] Thin and intertriginous skin responds to lower potencies and thick hyperkeratotic areas such as the palms and soles require high potency agents. Infants have a large body surface area that increases the chance of systemic absorption and adverse events, such as adrenal suppression.[3] In general, very high potency agents should be avoided in children, if possible, or used sparingly in combination or rotation

with steroid sparing alternatives such as coal tar, anthralin, calcipotriene and topical calcineurin inhibitors.

Coal Tar

Crude coal tar has antipsoriatic, antiseborrheic, antipruritic and keratolytic effects.[4] Given its better cosmetic acceptability, liquor carbonis detergens (LCD), a modified, less clinically active coal tar, has largely replaced crude coal tar in the outpatient setting. It can be compounded in an ointment, cream or solution vehicle in concentrations from 0.5% to 20%. Tar is a safe, effective treatment for childhood psoriasis and is supplied in a variety of topical formulations and shampoos. It can be used alone or compounded with corticosteroids, lactic and salicylic acid. Its safety, efficacy, and relatively low cost, compared with other topical agents are advantages in the long-term treatment of psoriasis. Side-effects of tar include folliculitis, irritation, and photosensitivity. It should not be used on acutely inflamed skin, or on pustular or erythrodermic psoriasis.[5] There is no definitive evidence of an increased risk of skin cancer above the expected incidence for the general population from the use of therapeutic tar.[6,7] Education regarding the favorable safety profile and place in therapy as a steroid-sparing adjunct may increase tolerance and compliance of this excellent and underutilized topical therapy.

Anthralin

Anthralin (dithranol) is a potent anti-inflammatory and anti-proliferative agent.[8] It is a synthetic version of chrysarobin, a natural substance derived from the araroba tree of South America used to treat psoriasis for nearly 100 years.[9] Negligible systemic absorption is responsible for its excellent safety profile and ease of use, especially in children. Its use has been limited due to staining and irritation, but short contact and "minutes" therapy are popular, less messy alternatives (increasing concentrations [0.1% to 3%] of dithranol applied to the skin and left in place for 10-30 minutes daily until a slight irritation develops, then hold dose/time until clear[10]). Lower concentrations or less contact time should be maintained on more sensitive sites such as anogenital skin.

Calcipotriene

Calcipotriene (calcipotriol in Europe and Canada) is an analog of vitamin D_3 that has been proven safe and effective in adults with psoriasis. It is an efficient nonsteroidal alternative and has utility as monotherapy as well as in novel sequential and rotational combinations with topical steroids.[11] Calcipotriol ointment has been shown to be effective, well tolerated and safe in children with psoriasis, with local irritation the most commonly reported side-effect.[12-15] Adverse effects of topical calcipotriol on systemic calcium homeostasis in adult patients with chronic plaque psoriasis has been evaluated and is related to dose per unit body weight of the patient.[16] Though no formal guidelines exist for children, use of up to 45g/week per m^2 in children does not seem to influence serum ionized calcium levels.[13] Regimens combining calcipotriene and topical steroids, such as once daily use of each or twice daily use of calcipotriene on weekdays and steroids on weekends only, are steroid sparing and superior in efficacy to twice daily monotherapy with either agent.[17,18] Calcipotriene destabilizes in the presence of salicylic acid, ammonium lactate, and hydrocortisone valerate 0.2% ointment and thus, should not be used at the same time as or compounded with these molecules.[19]

Tazarotene

Tazarotene is a third-generation topical retinoid US FDA-approved for once daily treatment of psoriasis in adults aged 18 and older and acne vulgaris in patients aged 12 and above. Similar to other retinoids, tazarotene restores normal epidermal differentiation and proliferation and reduces epidermal inflammation.[20] Limit its use to thicker plaques on non-intertriginous sites. Tazarotene is neither sensitizing nor phototoxic, but dose-related skin irritation is common and often necessitates combination with a topical steroid applied at a different time of day. Short contact (10-60 minutes per day, then wash off), alternate day or weekly applications are potential ways to include this useful agent in sequential and rotational regimens. Effectiveness of tazarotene for nail psoriasis has been demonstrated clinically in adults[21] and children.[22]

Topical Calcineurin Inhibitors

Tacrolimus and pimecrolimus are nonsteroidal immunomodulating macrolactams that work by blocking the enzyme calcineurin, ultimately inhibiting the downstream production of IL-2 and subsequent T-cell activation and proliferation.[23] Both topical agents are currently FDA approved for second line intermittent treatment of atopic dermatitis in patients aged 2 years and older (pimecrolimus and tacrolimus 0.03%) and aged 15 and older (tacrolimus 0.1%). They are effective, safe and well tolerated therapeutic options for psoriasis at sites more sensitive to the long-term adverse effects of topical steroids such as the face, flexures, and anogenital region.[24-27]

Salicylic Acid

Salicylic acid is a useful adjunctive keratolytic agent for very thick localized plaques arising on the scalp, palms and soles. It should be used sparingly and with caution in the pediatric population because of the risk of percutaneous salicylate intoxication.[28] Avoid its use altogether in infants and children less than 6 years old.

Conclusion

Treatment of childhood psoriasis is both challenging and rewarding. Medical management remains primarily anecdotal as most therapies are neither studied nor approved for use in children. At our disposal are both traditional and new topical agents that can be used in diverse ways as monotherapy or in combination. Treatment decisions must be individualized for each patient based on thorough assessment of the disease, comorbidities, and impact on quality of life.

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Advances in Pemphigus Therapy

V. Prajapati; P. R. Mydlarski MD, FRCPC

Division of Dermatology, Department of Medicine, University of Calgary, Calgary, AB, Canada

ABSTRACT

The pemphigus variants represent a group of potentially life-threatening autoimmune mucocutaneous blistering diseases. Though systemic corticosteroids have dramatically reduced the rate of disease mortality, current therapeutic options are limited by their toxicity profiles. Advancements in our understanding of the molecular mechanisms involved in the pathogenesis of pemphigus have translated into the development of novel therapies. However, few treatments have been subject to randomized controlled trials to firmly establish therapeutic efficacy. Herein, we focus on the new and emerging therapies in the management of pemphigus.

Key Words: pemphigus, autoimmune skin disease

Pemphigus represents a group of rare autoimmune mucocutaneous blistering disorders. The 2 main subtypes are pemphigus vulgaris (PV) and pemphigus foliaceus (PF), each with its own clinical variants. Less common forms include paraneoplastic pemphigus, IgA pemphigus, and pemphigus herpetiformis. Since PV is the most common subtype of pemphigus worldwide, it will be the focus of this article.

PV affects both genders equally and has a mean age of onset of 50-60 years. A higher prevalence has been noted in individuals of Ashkenazi Jewish, Mediterranean, Northern Indian and Persian descents.[1] Patients often present with multiple, painful erosions or flaccid bullae on the skin and/or mucous membranes. Mucosal disease precedes cutaneous involvement in the majority of the cases.[2]

The disease is mediated by circulating immunoglobulin G (IgG) autoantibodies against the desmosomal cadherins, desmogleins 1 and 3.[3] Histopathology reveals a loss of cell-cell adhesion (acantholysis) in the suprabasilar layer of the epithelium and direct immunofluorescence (DIF) of perilesional skin reveals intercellular deposition of IgG +/– C3. As antibodies often correlate with disease activity, indirect immunofluorescence (IIF), immunoblots, and enzyme-linked immunosorbent assays (ELISA) are commonly used to quantify circulating antibody levels.[4]

If left untreated, PV is frequently fatal with a mortality rate ranging from 60% to 90%.[5-8] While systemic corticosteroid use and other therapeutic advances have reduced this mortality rate to approximately 10%, complications from treatment are now the primary cause of morbidity and mortality in this population.[6,7] The goal of managing pemphigus patients is, therefore, to induce and maintain remission with the lowest possible doses of medication, so as to minimize the risk of serious and potentially fatal adverse effects.[2]

Conventional Therapies

Systemic corticosteroids remain the treatment of choice for pemphigus as they are both effective and capable of inducing a rapid remission. However, adverse effects of corticosteroids are both time- and dose-dependent.[9] They include weight gain, diabetes, hypertension, glaucoma, cataracts, osteoporosis, avascular necrosis, peptic ulcer disease, adrenal insufficiency, electrolyte and lipid abnormalities, psychosis, immunosuppression, and increased susceptibility to infections.[9] Adjuvant therapies are, therefore, used to provide a steroid-sparing effect. As these treatments typically have a slower onset of action (i.e., 4-6 weeks), they are most beneficial as maintenance therapies. Conventional adjuvants include various immunosuppressive agents such as azathioprine, mycophenolate mofetil, methotrexate, cyclophosphamide, chlorambucil and cyclopsorine, as well as anti-inflammatory agents such as gold, dapsone, colchicine and a variety of tetracycline antibiotics (Table 1).[2,4,10] Unfortunately, these medications are often associated with significant toxicities and must be used with caution. Though the majority of patients will ultimately respond to conventional therapies, few patients develop recalcitrant disease.

Emerging Therapies

Over the years, advances have been made to expand our therapeutic armamentarium for pemphigus. Emerging therapies include intravenous immunoglobulin (IVIg), plasmapheresis, immunoadsorption (IA), extracorporeal photochemotherapy (ECP), rituximab, tumor necrosis factor-alpha (TNF-α) antagonists (infliximab and etanercept), cholinergic agonists, and other experimental therapies such as desmoglein 3 peptides and KC706.

Intravenous Immunoglobulin (IVIg)

IVIg is a fractionated and purified blood product derived from the plasma of between 1,000 and 15,000 healthy donors per batch.[4] It contains a high concentration of IgG and has a broad range of antibodies directed against pathogens, foreign antigens, and self-antigens.[11] Although its exact mechanism of action remains unclear, IVIg is associated with a rapid and selective decline in the serum levels of pathogenic PV autoantibodies.[12]

Three case series and 1 retrospective analysis document the efficacy of IVIg in PV.[13-16] The dosage and frequency of IVIg infusions were comparable between the studies. In all 4 studies, treatment with IVIg resulted in a rapid

Drug Type	Systemic Agent	Mode of Administration	Dose
Systemic Corticosteroids	Prednisone	Oral	1-2mg/kg/d
	Dexamethasone	Oral or IV pulse	50-200mg/d for 3-5 d
	Methylprednisolone	IV pulse	500-1,000mg/d for 3-5 d
Immunosuppressive and Anti-inflammatory Agents	Azathioprine	Oral	3-4mg/kg/d
	Chlorambucil	Oral	0.05-0.2mg/kg/d
	Colchicine	Oral	1.2-1.8mg/d
	Cyclophosphamide	Oral	2-3mg/kg/d
		IV pulse	0.5-1g/m^2 monthly
		Immunoablative high-dose (IV)	50mg/kg/d for 4 d
	Cyclosporine	Oral	2-5mg/kg/d
	Dapsone	Oral	50-200mg/d
	Erythromycin	Oral	1,200mg/d
	Gold	IM injection	25-50mg/biweekly
		Oral	6-9mg/d
	Leflunomide	Oral	20mg/d
	Methotrexate	Oral, SC, IM or IV	5-30mg/wk
	Minocycline	Oral	100-200mg/d
	Mycophenolate mofetil	Oral	30-45mg/kg/d
	Tetracycline +/- Nicotinamide	Oral	1-2g/d 1,500-2,000mg/d
Biologic Agents	Etanercept	SC injection	50mg weekly
	Infliximab	IV infusion	5mg/kg/cycle
	Intravenous Immunoglobulin (IVIg)	IV infusion	2g/kg/cycle
	Rituximab	IV infusion	375mg/m^2 weekly for 4 weeks; OR 1,000mg on days 1 and 15†

Table 1: Therapeutic doses for immunomodulatory drugs used in the treatment of pemphigus.
IV = intravenous, IM = intramuscular, SC = subcutaneous
† Weight-independent dosing schedule based on unpublished observations.

clinical response and a corticosteroid-sparing effect.[13-16] In 2 retrospective analyses, however, IVIg demonstrated a less favorable response.[17,18] As the published studies are limited by their methodologies and small sample sizes, a Canadian multi-centre randomized controlled trial is underway to establish the role of IVIg in the management of PV patients.

Plasmapheresis

Plasmapheresis is the process by which plasma is removed from blood using a cell separator. The blood cells and an appropriate plasma substitute are then returned to the patient undergoing treatment. As antibodies are contained within plasma, plasmapheresis results in the removal of the pathogenic PV autoantibodies. In a multicenter study, PV patients (n=40) were randomized to receive prednisolone alone or prednisolone plus large-volume plasma exchange.[19] While plasmapheresis failed to demonstrate a therapeutic benefit in this study, it has been suggested that an additional immunosuppressive (i.e., cyclophosphamide) or immunomodulatory (i.e., IVIg) therapy may be required to prevent the rebound production of pathogenic autoantibodies associated with disease flares.

Multiple case series have evaluated the efficacy of plasmapheresis in treating PV.[20-23] Of the 28 patients evaluated in these studies, 18 (64%) experienced complete remission, 6 (33%) experienced partial remission and 4 (22%) had no clinical improvement. Adverse effects encountered included systemic infections, acute hepatitis, thrombocytopenia, anemia, hypocalcemia, nausea, dizziness, urticaria, fever, and hypotension.[20-24]

Immunoadsorption (IA)

IA consists of collecting patient plasma, passing it through an adsorber column (i.e., Protein A) to remove circulating immune complexes and IgG and then returning the filtered plasma to the patient.[25] Four case series and 2 case reports document the efficacy of IA for the treatment of recalcitrant PV.[26-31] Though patients were allowed to remain on concomitant immunosuppressive therapies, IA resulted in a dramatic clinical response and a rapid decline in desmoglein-specific IgG autoantibodies.[26-31] In the study by Schmidt, et al., a corticosteroid-sparing effect was observed.[27] More recently, a small case series demonstrated that IA, administered in combination with rituximab, may result in long-term remission.[32] In all studies, IA was safe and well tolerated.

Extracorporeal Photochemotherapy (ECP)

In ECP, also known as photopheresis, a patient's white blood cells are collected (leukapheresis), exposed to 8-methoxypsoralen, irradiated with ultraviolet-A light and reinfused into the patient. The proposed mechanism of action may involve inhibition of pathogenic autoantibody production by B lymphocytes.[10] There are only 2 small case series and 2 case reports in the literature that document the use of ECP for refractory PV.[33-36] Of the 9 PV patients treated with ECP in these studies, all experienced significant clinical improvement, and no adverse effects from ECP were noted.

Rituximab

Rituximab is a chimeric murine/human IgG_1 anti-CD20 monoclonal antibody that targets pre-B and mature B lymphocytes, resulting in complement and antibody-dependent cytotoxicity and apoptosis. Rituximab reduces circulating B cells, thereby preventing their maturation into antibody-producing plasma cells. Multiple case reports suggest that rituximab is an effective treatment option for PV.[37] Of the 18 patients with refractory PV reviewed, 3 (17%) experienced complete remission, 4 (22%) experienced clinical remission with further therapy required and 11 (61%) experienced partial remission. Systemic infections occurred in 4 of the 18 patients, resulting in 1 fatal outcome.

The largest clinical study evaluating the use of rituximab in PV has been a case series of 14 patients with refractory PV in which 12 (86%) experienced a complete remission at 3 months after a single cycle of rituximab.[38] This agent was also shown to be effective when used in combination with IVIg. In a series of 11 patients with extensive, recalcitrant PV, 9 (82%) experienced a clinical remission lasting between 22-27 months with combination therapy.[39]

Tumor Necrosis Factor-alpha (TNF-α) Antagonists

TNF-α antagonists may be beneficial for the treatment of PV as experimental studies have demonstrated that TNF-α plays a role in the acantholytic process.[40,41] Two case reports document the successful use of infliximab for refractory PV.[42,43] Two additional case reports have shown clinical improvement of PV with the use of etanercept.[44,45] Clinical trials for both infliximab and etanercept are currently underway.

Cholinergic Agonists

Research suggests that acetylcholine and its receptors are involved in the acantholytic process of pemphigus.[2] To date, only 2 clinical studies have been performed.[46,47] In a case series of 6 patients with active PV, 3 (50%) experienced clinical improvement with the cholinergic agonist pyridostigmine bromide (Mestinon®, Valeant Pharmaceuticals).[46] Two of the 3 responders were able to control their disease with pyridostigmine bromide alone and 1 patient was able to remain in remission without any medications. In a recent double-blind, placebo-controlled trial of 3 PV patients with a total of 64 lesions, those lesions treated with 4% pilocarpine gel were found to have a significantly higher epithelialization index compared with placebo.[47]

Other Experimental Therapies

Selective therapy using intravenous desmoglein 3 peptides was developed to suppress the production of anti-desmoglein 3 antibodies through inactivation and/or deletion of disease-associated CD4+ T lymphocytes.[48] However, an open-label phase I clinical trial of PI-0824 failed to demonstrate significant changes in anti-desmoglein 3 antibody titres following treatment with 2 IV infusions of desmoglein 3 peptides.[48]

A novel therapy, KC706 (Kémia, Inc.) is an oral allosteric p38 mitogen-activated protein kinase (p38MAPK) inhibitor. In a murine model of pemphigus, p38MAPK inhibition prevented blister formation.[49] A clinical trial is underway to determine the safety and efficacy of KC706 in the management of PV.

Conclusion

While corticosteroid therapy remains the mainstay of treatment for PV, the morbidity associated with its use is significant. Conventional immunosuppressive and anti-inflammatory therapies are further associated with serious and potentially life-threatening adverse events. With an improved understanding of PV pathogenesis, a number of novel therapies have been developed. Though many of these therapies appear promising, case reports and case series dominate the dermatologic literature. Randomized controlled trials are urgently required to establish their efficacy and safety in the management of pemphigus patients.

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Class	Name/Company	Approval Dates/ Comments
Melanoma	**Peginterferon alfa-2b** *PEG-Intron*™ Schering-Plough	The US FDA accepted for review a supplemental Biologics License Application in January 2008 for this recombinant alfa interferon, and has granted Priority Review status for the adjuvant treatment of patients with Stage III malignant melanoma.
Melanoma	**Elesclomol** (formerly STA-4783) Synta Pharmaceuticals/ GlaxoSmithKline	The US FDA granted orphan drug designation in January 2008 to this novel small molecule. By elevating oxidative stress levels, the agent triggers apoptosis by sensitizing cancer cells to agents that induce cell death through the mitochondrial pathway. In combination with paclitaxel, it is presently in Phase III clinical trials for the treatment of metastatic melanoma.
Dermal Filler	**Hyaluronic Acid Gel + Lidocaine** *Prevelle Silk*™ Mentor Corporation/ Genzyme Corporation	The US FDA approved this dermal filler in March 2008 for the reduction of moderate-to-severe facial lines, folds, and wrinkles. A controlled clinical study showed that the addition of lidocaine significantly relieved injection site pain.

Drug News

Melanoma	The rise of cutaneous melanoma (CM) has been steadily recorded by cancer registries over the past several decades. Although the causal relationship with other forms of skin cancer can be traced to exposure to levels of ultraviolet radiation, in CM, this distinct relationship cannot be established. Genetic influences appear to represent the best indicator in assessment of risk. In addition, photochemotherapy with 8-methoxypsoralen combined with ultraviolet-A radiation (PUVA), which is used to treat psoriasis and vitiligo, has also been found to be a potentiating factor. Psoralens, a form of furocoumarins, occur naturally in botanical sources that include vegetables and fruits (of particular interest is the citrus variety), and are known to exert photocarcinogenic effects that induce DNA damage. Under normal dietary conditions, exposure levels do not spawn phototoxic effects. The hypothesis, offered by Sayre, et al.*, is that one of the contributing factors to the increased incidence of CM may be attributable to the elevated intake of food sources containing photocarcinogenic furocoumarins. This suggestion follows from a recent large study of nurses where a positive association was found between citrus consumption and the development of CM. *Sayre RM, Dowdy JC. The increase in melanoma: are dietary furocoumarins responsible? *Med Hypotheses* 70(4):855-9 (2007 Sep 17).
US FDA Proposed Guidance	The US FDA released a draft guidance to industry on "Good Reprint Practices" for the distribution of medical or scientific journal articles and reference publications that contain information regarding unapproved uses of US FDA-approved drugs and medical devices. The FDA recognizes the contribution of off-label uses of products to medicine; however, the regulatory body is compelled to also implement safeguards against the promotion of unapproved uses. Recommendations contained in the draft guidance include: • Literature for dissemination should be published by an organization that has an editorial board. • The publisher should provide full disclosure of any conflicts of interest or biases for all authors, contributors, and editors associated with the publication. • Production should include a peer-review process and adhere to specific procedures outlined within this draft guidance. Supplements or publications that are funded by manufacturers of the product described in an article, especially those where the content is unsupported by credible medical evidence, may be considered as false or misleading and the US FDA will recommend against distribution of such material. The US FDA reserves the legal authority to determine if distribution of an article or publication constitutes promotion of an unapproved "new use", or whether such activities cause a product to be considered misbranded or adulterated under the Federal Food, Drug and Cosmetic Act. More details on this proposal can be found at: http://www.fda.gov/bbs/topics/NEWS/2008/NEW01798.html.