

The Use of Cyclosporine in Dermatology

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ABSTRACT

Cyclosporine is an immunosuppressive drug that acts selectively on T-cells by inhibiting calcineurin phosphorylase. It has been used in dermatology since its approval for US Food and Drug Administration in 1997 for the use in psoriasis. While indicated only for the treatment of moderate to severe psoriasis, cyclosporine has also been used as an off-label drug for the treatment of various inflammatory skin conditions, including atopic dermatitis, blistering disorders, and connective tissue diseases. In this article, we review the use of cyclosporine in dermatology.

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INTRODUCTION

Cyclosporine is a cyclic polypeptide immunosuppressant agent consisting of 11 amino acids. It forms a complex with cyclophilin, a cytoplasmic immunophilin. This complex inactivates calcineurin phosphorylase, preventing the phosphorylation of nuclear factor of activated T-cells (NFAT) and, therefore, the production of NFAT-dependent cytokine such as interleukin-2, which is required for full activation of the T-cell pathway. Cyclosporine was the first immunosuppressive drug found to act selectively on T-cells. It was isolated in 1970 from the soil fungus *Tolypocladium inflatum Gams* by Borel at Sandoz Laboratories in Basel, Switzerland, while looking for novel antifungal agents.[1]

In 1979, cyclosporine was first observed to improve psoriasis during a pilot study undertaken to investigate the efficacy of cyclosporine in rheumatoid arthritis and psoriatic arthritis,[2] but was not approved by the US Food and Drug Administration for the treatment of psoriasis until 1997. Since then, the FDA has not approved cyclosporine for the treatment of any other clinical condition in dermatology; however, it has been approved for use in atopic dermatitis in other countries (Europe) and it has been used off-label for the treatment of multiple inflammatory skin conditions including blistering disorders, and connective tissue diseases.

Cyclosporine in Psoriasis

Nowadays, even in the age of biologics, cyclosporine remains as one of the most effective treatments for psoriasis because of its efficacy and rapid onset of action. Multiple dose-finding studies have been performed in order to elucidate the optimal dose for cyclosporine that achieves clearance with minimal toxicity.[3-7] The initial dose of cyclosporine recommended by the American Academy of Dermatology is 2.5 mg per kg daily, administered in two divided doses (every twelve hours). In patients with severe psoriasis, in which a rapid response is needed, an initial dose of 5 mg per kg daily is usually a better option. Although the higher dose is associated with a faster and more efficacious response, it is also associated with a higher rate of adverse reactions. Clinical improvement of the cutaneous lesions occurs after approximately 4 weeks, and maximum response is seen after 8 to 16 weeks. If a satisfactory response is not achieved after 4 to 6 weeks of initial therapy with the lower dose (2.5 mg per kg daily), the dose can be increased gradually by 0.5 to 1.0 mg/kg/day at 2- to 4-week intervals, to a maximum of 5 mg/kg/day, as long as, the laboratory parameters remain satisfactory.[8] If response is still unsatisfactory after 3 months of treatment with the higher doses, then cyclosporine should be discontinued.

Long-Term Therapy

Currently, long-term therapy of psoriasis (> 1 year) with cyclosporine is not a common approach and should be prescribed only after other therapeutic options have been considered. This is because of possible adverse effects, including renal toxicity and arterial hypertension.[9,10] There is also the possibility for an increased risk of developing lymphoproliferative disorders and other malignant tumors, especially squamous cell carcinomas of the skin (more common in patients with high cumulative doses of phototherapy in combination with psoralen–UV-A (PUVA) (>1000 J per cm^2).[11,12] Current guidelines limit the continuous use of cyclosporine in the United States to 1 year,[13] whereas in Europe the recommended limit is 2 years.[8,14]

Short-Term Therapy

The use of intermittent short-term therapy is currently the most commonly recommended regimen of cyclosporine for the treatment of psoriasis.[8,13,15-17] Patients are treated until an adequate response is achieved, which generally requires 8 to 16 weeks. Subsequently, cyclosporine is discontinued or slowly tapered by 1 mg per kg every week over 4 weeks[9].

A short course of cyclosporine can be used in severe flares of psoriasis because of its rapid onset of action until a better long-term alternative treatment is instituted. This is particularly useful in the treatment of erythrodermic or generalized pustular psoriasis where cyclosporine remains as the treatment of choice despite the new biologic medications.[8,13,18]

Combination Therapy

The goal of combination therapy in psoriasis is to increase the efficacy of the treatments while reducing their toxicities,[19] which is especially important in the case of cyclosporine, as its complications, such as hypertension and nephrotoxicity, are dose-related.

Cyclosporine has been used effectively in combination with multiple topical therapies including topical corticosteroids,[20,21] vitamin D3 analogues,[22] and anthralin.[23] These combinations are safe and effective as topical therapies improve the response to cyclosporine allowing reduction of the cyclosporine dose and its associated toxicity.

In contrast to topical agents, the combination of cyclosporine with phototherapy is more controversial. Although cyclosporine has been combined with ultraviolet B,[24] and PUVA,[25,26] there is an increased risk of skin cancer (squamous cell carcinomas). Therefore, the combination with these therapeutic modalities should be avoided, whenever possible.[27,28]

Cyclosporine has also been combined with other systemic therapies such as acitretin, methotrexate, mycophenolate mofetil, and biologics to achieve greater efficacy and safety. Among these, the most extensively studied are the combination of cyclosporine with Biologics and Methotrexate. The use of cyclosporine with methotrexate is controversial because cyclosporine is nephrotoxic and methotrexate is excreted by the kidneys, and because methotrexate is hepatotoxic and cyclosporine is metabolized by the liver. However, several studies using this combination for psoriasis and psoriatic arthritis seem to demonstrate benefits without a significant increase in side effects, at least with a short-term treatment.[29-34]

The combination with Acitretin has not evidenced additional benefits,[45] and in these cases a careful monitoring of triglycerides is warranted, as both agents alone can cause hypertriglyceridemia. This combination may play a role in the treatment of patients with multiple squamous cell carcinomas, as low doses of Acitretin have showed efficacy in preventing recurrences of the skin cancer.[35,36]

The combination with biologics has been discussed extensively in the literature, but the long-term risks and side effects are not well studied.[37-39] Opportunistic infections have been reported in patients treated with biologics in conjunction with other systemic immunosuppressive agents.[40] Therefore, it is advisable to minimize the overlap period.

Although not optimal for the treatment of psoriatic arthritis, there is some evidence of benefit with the use of cyclosporine, either alone or in combination with methotrexate.[41,42]

Adverse Drug Reactions/Safety

The most frequently reported adverse effects associated with the use of cyclosporine as short term in dermatology (maximum dose 5 mg per kg) including increases in serum creatinine, increase in blood urea nitrogen, arterial hypertension, decreased magnesium, increased bilirubin, increased liver enzymes, gingival hyperplasia, paresthesias, headache, muscle aches, and generalized hypertrichosis.[6]

Other adverse effects have also been reported in long-term studies including the developed of lymphoproliferative disorders and other malignant tumors.[43] However, the majority of these studies did not evaluate the risk in the general population or in psoriasis populations and did not evaluate the patients for years after discontinuation of the drug. The largest study (over 1200 subjects) evaluating the long-term safety of cyclosporine in dermatologic patients concluded that there was no evidence that cyclosporine at dermatologic doses (maximum 5 mg/kg/day) with no additional immunosuppresion increased the risk of lymphomas or internal malignancies.[44] However, the same study demonstrated a significant increase in the incidence of non-melanoma skin cancers (especially squamous cell carcinomas). Another adverse event associated with the long-term treatment is the developed of opportunistic infections. Like other immunosuppressive therapies, cyclosporine may increase the risk of various bacterial, parasitic, viral, and fungal infections, as well as the risk of infections with opportunistic pathogens.

Summary

In our opinion, even with recent developments of new therapeutic modalities, cyclosporine remains an effective systemic therapy for moderate to severe psoriasis. Current American Academy of Dermatology guidelines suggests that intermittent therapy with cyclosporine for psoriasis is preferable to long-term treatment. In long-term therapy, the risks and benefits for each individual patient must be weighed carefully due to adverse drug reactions, especially nephrotoxicity and increases in blood pressure, as well as a potentially increased risk of non melanoma skin cancer. In cases in which long-term treatment is needed, the duration of continuous treatment should not exceed 1 year whenever possible.

Atopic Dermatitis

Atopic dermatitis (AD) is a chronic relapsing skin disease. Therefore successful treatment of AD requires systematic, multifaceted approach incorporating skin hydration, pharmacologic therapy and identification and elimination of trigger factors. In patients refractory to conventional forms of therapy, anti-inflammatory and immunosuppressive agents may be necessary.[45]

Cyclosporine has been recommended by the AAD as being effective for the treatment of atopic dermatitis refractory to conventional therapy. Unfortunately there is no statement as to the recommended dosage although the dosage employed for psoriasis is conventionally used. Cyclosporine has been used widely in adults and children with AD.[1]

Cyclosporine had been shown to reduce the numbers of helper/inducer T-cells and the number of activated cells expressing Interleukin-2 (IL-2), IL-4, and IL-5. It also inhibits the growth and differentiation of B-lymphocytes and the functional activities of mononuclear phagocytes, Langerhan's cells, and eosinophils. Furthermore, recently immunohistochemical study showed that cyclosporine may play a therapeutic role via effects on the cutaneous nervous system through altered innervations and neuropeptide expression in lesional skin of AD. In addition to these, cyclosporine inhibits mast cells (MC) activation by altering the topographical relationship between MCs and the cutaneous nerves in lesional skin, suggesting a new aspect of the effects of cyclosporine in the management of the DA.[46]

In terms of cyclosporine dosage, some studies suggested the dose of 5 mg/kg/day for 2 weeks with gradual tapering as dictated by the clinical response over the ensuing 3 months to a dose of 1.5 mg/kg/day. Other studies had reported a starting dose of 1.0 mg/kg/day to 4.2 mg/kg/day and whenever possible dosing titrated to a minimal clinically effective dose. In general these dosages showed an objective decrease in 50% of the lesions at 6 to 8 weeks of treatment correlated with the improvement in the disease severity score, lichenification score, disease extent score, itch, loss of sleep, and overall benefit in the quality of life.

The response with the use of higher dose is faster than with the lower dose when cyclosporine is used as a short-term treatment in crisis intervention for AD.[47]

There are studies showing that cyclosporine can be used intermittently, but when comparing these studies with those using continuous therapy, the results showed more consistent results (long term remission) when the continuous therapy had been used.[1,48]

Similar to psoriasis, when maintenance therapy is needed, the lowest effective dose should be used to ensure maximum safety.[1,47]

Most of the trials concluded that using the continued and low-dose therapy has been safe and effective for the long-term treatment of atopic dermatitis in children and adults. Close follow up and routine laboratory monitoring must be performed.[1,46,48,49]

In regards to withdrawal of cyclosporine treatment, Granlund et al showed rapid relapses within 2 weeks after discontinuation of therapy (50% of the patients); other studies have found high incidence of relapse, however, the time to relapse was longer. Harper found 86% of relapses after 9 months of discontinuation of treatment and Atakam and Erdem reported 75% of patients relapsed at 24 weeks post cyclosporine treatment. Thus, there is an expectation that the disease will worsen upon cessation of cyclosporine. However, the extent of disease and symptoms scores remain better than at baseline in the post treatment period, suggesting a possible sustained remission in some patients.[1,46]

Schmitt et al, showed in a meta-analysis that there was no evidence of a rebound phenomenon on withdrawn of cyclosporine, but there are isolated retrospective studies that did report a rebound phenomenon in a small number of patients.[1]

Chronic Urticaria

Urticaria is a cutaneous vascular reaction induced by immunological and nonimmunological mechanism. The mainstays for the treatment of chronic urticaria are antihistamines and occasionally short courses of corticosteroids.

Cyclosporine may be used for the treatment of severe chronic idiopathic urticaria as an alternative to corticosteroid therapy, either as a steroid-sparing agent or as monotherapy in chronic urticaria that is refractory to corticosteroid therapy.[1,50]

Guidelines from the British Association of Dermatology have recommended cyclosporine for the treatment of severe chronic idiopathic urticaria to be unresponsive to antihistamines, while stating that optimal patient selection, dose, and duration of treatment remain to be defined. However, long term use of cyclosporine is not recommended.[1]

A study reported by Tsutomu in 2010, showed in all of the patients, activated B cells (CD19+, CD23+ cells) and among the CD19+ cells, 20% were CD5+. Serum IL-2, TNF-α, and IL-5 levels of patients before cyclosporine treatment were statistically higher than those of the control group and after 4 weeks of cyclosporine therapy, IL-2, TNF-α, and IL-5 levels were significantly decreased.[51,52]

In the last decade, cyclosporine was reported to be beneficial in 27 studies, some of which were doubled-blind controlled studies. In some of them the dose of cyclosporine was between 4 mg/kg/day to 5 mg/kg/day whereas a low dose (2 mg/kg/day to 3 mg/kg/day) was given in other studies. When lower dose of cyclosporine was administered (2 mg/kg/day to 3 mg/kg/day, most studies reported a very low incidence of side effects (mostly gastrointestinal or peripheral neuropathy).[51,52] In all of these studies, the responses indicated clinical improvement.

Consequently, when lower doses of cyclosporine treatment (2.5 mg/kg/day) were given for 4 weeks, it lowered the serum levels of IL-2R, IL-5, and TNF-α, which are frequently increased in patients with chronic idiopathic urticaria.[1,50]

There are other studies that have attempted to answer not only the question of the dose but also the duration of cyclosporine treatment for chronic urticaria. Several authors recommended a starting dose between 3 mg/kg/day to 5 mg/kg/day for 6 weeks followed by 3 weeks at 2 mg/kg/day and then 3 weeks at 1 mg/kg/day before discontinuing. That regimen has resulted in remission or significant improvement while maintaining a good safety profile.[1]

Tsutomu recently evaluated the effectiveness of cyclosporine treatment in chronic idiopathic urticaria (CIU). Some studies showed that high CIU activity can be associated with an elevated high sensitivity C-reactive protein (HS-CRP) and a decreased basophil counts. Patients with CIU and elevated CRP levels had a significant decrease in CRP levels as the urticaria improved with cyclosporine treatment.[51]

Kessel and Toubi also reported, good results for chronic urticaria with low-dose cyclosporine (3/mg/kg/day). They used this dose for 2 months and then the dose was gradually decreased to 2 mg/kg/day and 1 mg/kg/day during the following month and concluded that it is an effective and safe therapy regimen. They also suggested that in a small subgroup of patients, long-term therapy could be necessary, and it is considered relatively safe.[52]

In this study the rate of infections with Epstein Barr virus and cytomegalovirus was the same as would be expected in a normal population. Also the rates for malignancy would be expected to be low as long as the levels were kept at or below 50 ng per mL. They concluded that when cyclosporine is required for longer periods (5 to 10 years) for the treatment of CIU, the goal should be to keep the dose between 1 mg per kg to 1.5 mg per kg.[51]

Prurigo Nodularis

Prurigo nodularis is an idiopathic condition consisting of nodular cutaneous lesions that itch intensely. It is a reaction associated with a marked proliferation of sensory nerve fibers associated with severe itch. Although some acute forms may be induced by insect stings, most of the subacute and chronic forms appear to be idiopathic. Several metabolic, psiquiatric, infectious, and malignant disorders may be associated with prurigo nodularis lesions.[1,53]

The treatment for prurigo nodularis is extremely unsatisfactory. Currently, treatments include topical antipruritics, topical steroids, intralesional steroids, psoralen plus Ultraviolet A light phototherapy, ultraviolet B light therapy, cryotherapy, azathioprine, chloroquine, dapsone, minocycline, thalidomide, topical vitamin D, and capsaicin.[1,53]

Cyclosporine may be considered a second line agent for this condition. Frequently, high dosages of 3 mg/kg/day to 4.5 mg/kg/day for 24 to 36 weeks are required. In some patients, significant improvement in the lesion and reduction of pruritus may be seen. Pruritus can be reduced as early as the first 2 weeks of therapy, allowing also the prurigo nodules to heal. In most reports showing that when cyclosporine dosage is reduced or discontinued the prurigo relapses.[53,54]

The mechanism of action of cyclosporine in nodular prurigo is believed to be similar to its action in atopic dermatitis.[53,55]

Neutrophilic Dermatosis

Pyoderma Gangrenosum

The use of cyclosporine as a second-line therapy in corticosteroid refractory pyoderma gangrenosum (PG), or as coadjuvant treatment, has been well documented with multiple cases reported in the last 2 decades. The immunomodulator and antinflammatory effects achieved with cyclosporine have proven to be effective in the management of this condition. Occasionally cyclosporine maybe of beneficial in secondary associated systemic diseases such as inflammatory bowel disease.[1,56,57]

Although there is no standard protocol for the treatment of PG with cyclosporine, the majority of cases of success reported in the literature were dosed with 5 mg/kg/day.[1,58,59]

It has been suggested that smaller doses may not be as effective.

Reich et al[58] and Soria et al[60] reported loss of efficacy as well as the development of new lesions, when oral doses were reduced from 5 mg/kg/day to 3 mg/kg/day. Nonetheless, some of their patients benefited equally from a lower dose (3 mg/kg/day).

Oral administration of cyclosporine was the most commonly prescribed, however, other authors have noted that giving cyclosporine IV at a dose drug of 3 mg/kg/day for 1 week,[61] or at 4 mg/kg/day for 1 to 3 weeks produce similar results.[62]

Formulations, other than systemic, have also been used for the treatment of PG. Azizan et al[63] treated 4 patients with topical cyclosporine with significant efficacy and without significant systemic absorption of the drug and no side effects. This may be an ideal therapeutic approach for localized disease and/or for PG cases that are not associated systemic conditions. This option may represent a safer alternative for very ill patients, thus preventing the potential of side effects associated with the systemic use of this drug.[63-65]

Once therapy is implemented, improvement of the inflammation surrounding the ulcer may be evident within 24 hours after starting treatment with peak improvement noticeable after 2 weeks. Measuring the efficacy of treatment is challenging, however, as these patients are usually concomitantly receiving other immunosuppressant drugs.

The incidence of relapse is very high despite initial improvement; nevertheless, cyclosporine may represent a more affordable option to treat PG in cases were treatment with other options such as biologics (infliximab, adalimumab) is not economically feasible.

Sweet's Syndrome

Sweet's syndrome, pyoderma gangrenosum, and subcorneal pustular dermatosis are neutrophilic conditions that have an inflammatory infiltrate consisting of mature polymorphonuclear leukocytes. The neutrophils are usually located within the dermis

in Sweet's syndrome and pyoderma gangrenosum, however, in subcorneal pustular dermatosis they are found in the upper layers of the epidermis. Sweet syndrome is also referred to as acute febrile neutrophilic dermatosis. It is a condition of unknown etiology characterized by pyrexia, elevated neutrophil count, painful erythematous cutaneous lesions, and usually prompt clinical improvement is seen following corticosteroid systemic therapy. The standard therapy for Sweet's syndrome is prednisone or prednisolone at an initial dose of 0.5 mg/kg to 1.5 mg/kg of body weight per day, and gradual reduction is recommended for the following 2 to 4 weeks. Sweet's syndrome can be associated with other conditions such as Acute Myeloid Leukemia (AML).

The tendency of Sweet's syndrome to relapse was the rationale for trying cyclosporine as a first-line treatment. Several cases have been reported demonstrating the efficacy of cyclosporine for the treatment of Sweet's syndrome.[66-70]

Cyclosporine had been used in 3 settings: as initial monotherapy, a second line therapy after the failure of other first-line treatments (steroids) or as a corticosteroid-sparing agent. The initial oral dose has ranged from 2 mg/kg/day to 4 mg/kg/day, to as high as 10 mg/kg/day for the acute presentation; this dose is continued for the first 10 days and then reduced gradually and discontinued at day 21. Patients should be closely monitored due to the side effects.[68,69]

Cyclosporine has been shown to inhibit neutrophil chemotaxis and, more importantly, impair neutrophil migration into infective and sterile inflammatory foci *in vivo*. Monocyte functions are also modulated by cyclosporine and it has been shown *in vitro* to inhibit antigen presentation and suppress monocyte activation. Even though, Sweet's syndrome is predominantly a neutrophilic, inhibition of cytokine release by mature T-helper lymphocyte and decrease of effector found in cytotoxic lymphocytes has been reported. The mode of acting of cyclosporine in this disease may be related to these effects.[66,69,70]

Furthermore, it has been suggested that interleukin 1 (IL-1) might play a key role in Sweet's syndrome. IL-1 possesses endogenous pyrogen activity, is chemotactic to neutrophils, induces neutrophil leucocytosis and stimulates synthesis of prostaglandin E2. Cyclosporine has been shown inhibit the release of Il-1.[70]

Cutaneous Lupus Erythematosus

Cutaneous lupus erythematosus includes wide variety of skin lesions. Discoid lupus erythematosus are erythematous, scaly papules and plaques on sun-exposed areas that can leave scarring; of these, fewer 10% will develop systemic disease. Systemic lupus erythematosus can produce malar erythema and widespread maculopapular lesions on the skin. Between these 2 entities, there is a wide spectrum of cutaneous manifestations: annular, psoriasiform (subacute lupus erythematosus), poikiloderma-like, lichenoid, panniculitis, verrucous, or bullous skin lesions.[71-73]

Cyclosporine has been used for concomitant treatment of systemic lupus erythematosus or as a third line therapy for cutaneous disease. In these settings cyclosporine is given after antimalarials, dapsone, oral prednisone, and/or retinoids have failed.[71] The recommended dose is between 2.5 mg/kg/day and 5 mg/kg/day, usually starting at a dose of 4 mg/kg/day to 5 mg/kg/day, and as the patient responds the dose can be decreased.[71]

In a clinical trial of 59 patients with systemic lupus erythematosus where other immunosuppressants failed, 75% improved when treated with cyclosporine, which included skin lesions, and patients were able to maintain the treatment for 2 years. Cyclosporine also improved lupus nephritis; thus there is no evidence of worsening the lupus associated renal disease. In some patients, however, it elevated the blood pressure; this is the most frequent reason for discontinuation of the therapy.[74]

In some cases, a combination of cyclosporine and other immunosuppressant drugs can allow a reduction in the dose of both medications, for example, the combination of cyclosporine and corticosteroids as a steroid-sparing agent[73]; cyclosporine and methotrexate have also been reported to be useful and safe,[75] though most of the reports are case series, and further controlled studies are needed.

Cyclosporine is also useful when lupus is associated with another inflammatory skin disease, such as lichen planus[76] or psoriasis.[77] Although these diseases have different clinical and histopathological features, cyclosporine has proven to be a beneficial treatment in many of them. Thus, cyclosporine can be used to treat refractory cutaneous lupus with or without systemic involvement. The recommended doses are between 2.5 mg/kg/day and 5 mg/kg/day and can be maintained for 2 years. Also, the combination with corticosteroids and other immunosuppressant drugs have proven to be beneficial.

Dermatomyositis

Dermatomyositis is an autoimmune disease of the skin and muscles. Skin lesions involve Gottron's papules, heliotrope rash, periungal telangiectasias, and/or facial erythema and edema.[78,79] The disease is usually associated with muscle weakness and elevated skeletal muscle enzymes. However, dermatomyositis sine myositis (or amyopathic, ie, without muscle involvement and with the characteristic skin lesions) is well recognized.[80] Prognosis is dependent upon the development of internal malignancy, interstitial lung disease, or clinical muscle weakness, which can be profound.

Cyclosporine is used to treat dermatomyositis as a steroid-sparing agent; the first-line therapy is glucocorticosteroids in high doses (1 mg to 2 mg/kg/day), usually associated with another immunosuppressant treatment like methotrexate or azathioprine. Cyclosporine can be and has been used as a second-line therapy,[81-83] and for refractory dermatomyositis unresponsive to methotrexate and azathioprine treatment. In a clinical trial com-

TABLE 1.

Skin Diseases in which Cyclosporine has Proved to be Useful

Disease	Cyclosporine Dose (mg/kg/day)	Response	Concurrent Drugs	Other Treatments Options	Comments	References	Level of Evidence
Alopecia Areata	5	Variable (25% to 76%)	Intravenous pulse of metilprednisolon	Corticosteroids, PUVA, immunosuppressant	Questionable risk to benefit ratio	88-91	III
Behçet Disease	5	Very Good	Prednisone	Corticosteroids, colchicine, dapsone, thalidomide, methotrexate, cyclophosphamide	Very effective for uveitis; not useful when neurological involvement	92-96	IIA
Granuloma Annulare	4	Very Good		Corticosteroids, PUVA, methotrexate	For disseminated forms that are non responders to other treatments	97	III
Eosinophilic Fasciitis	2	Variable	Prednisone	Corticosteroids, antimalarials, methotrexate, azatioprine, D-penicilamine	Isolated cases reported with good outcome	98-101	III
Hyperige Syndromes	3-5	Variable	Antibiotics	Corticosteroids, interferon gamma	Usually as a short time therapy in patients with recalcitrant disease	102-104	III
Lichen Planus	2,5-3	Very Good		Corticosteroids, topical tacrolimus, PUVA	Used in refractory cases; topical cyclosporine is useful in oral lichen planus	105-107	III
Lichen Plano Pilaris	4	Very Good		Corticosteroids, antimalarials	Effective when scarring alopecia has not developed	108,109	III
Lichen Sclerosus	3-4	Good		Topical corticosteroids, topical tacrolimus	All the patients were women with vulvar lichen sclerosus	110	III
Pemphigus Vulgaris	1-3	Good	Prednisone	Corticosteroids, azathioprine, cyclophosphamide	Used as steroid sparing agent, third line	111-115	III
Photosensivity Disorders: Polymorphic Luminic Eruption And Chronic Actinic Dermatitis	3-4,5	Good	Sunscreen	Sunscreen, phototherapy (to desensitize), azathioprine	In polymorphic light eruption cyclosporine can be used only during sunny months	116,117	III
Pityriasis Rubra Pilaris	2-5	Variable		Oral retinoids, methotrexate, phototherapy	Used in erythrodermic pityriasis rubra pilaris	118,119	III
Systemic Sclerosis	3,4-4,5	Variable		Corticosteroids, colchicine, methotrexate, azathioprine, mycofenolate mofetil	It can worsen renal disease.	120-122	III
Stevens Johnson Syndrome- Toxic Epidermic Necrolisis	5	Variable	Wound care, steroids.	Corticosteroids, intravenous immunoglobulin, anti TNF, cyclophosphamide, plasmapheresis	High doses of corticosteroids, or intravenous immunoglobuline are preferred	123-129	III
Cutaneous Vasculitis	2.5,5	Good	Topical corticosteroids	Colchicine, corticosteroids, azathioprine, methotrexate, cyclophosphamide, mycophenolate mofetil; plasmapheresis, rituximab	Third line	130-132	III

paring methotrexate and cyclosporine, methotrexate was more effective controlling the muscle disease but cyclosporine was better in the treatment of associated interstitial lung disease.[84] Several case reports of dermatomyositis with interstitial lung disease responding to cyclosporine and steroids can be found in the literature.[85] Cyclosporine is also useful when there is esophageal involvement,86 showing better results than other immunosuppressive agents.[84] In dermatomyositis sine myositis, cyclosporine can be useful, and there are cases showing good results.[80,85] Amyopathic dermatomyositis is often associated to lung disease, including interstitial pneumonia, pneumomediastinum, and pulmonary fibrosis; cyclosporine is recommended due to its favorable effects in the lung and the speed of action.[87]

The optimal dose of cyclosporine is between 1.8 mg/kg/day and 3.5 mg/kg/day combined with prednisone 1 mg/kg/day gradually tapered.[81,82]

Thus, cyclosporine can be used in dermatomyositis as a second line treatment as a steroid-sparing agent and is especially useful in patients with interstitial lung disease or esophageal involvement.

Other Diseases

There are many other skin diseases for which cyclosporine is a good treatment option (Table 1).[88-132] Most of these are series of cases and reviews of the literature (evidence III). There is an

overall lack of controlled trials with cyclosporine in these diseases, due to the fact that in most of the cases, cyclosporine was used as a third-line treatment after other options failed. There are also isolated case reports where cyclosporine has shown good results, including diseases such as granuloma annulare in its elastolytic form,[133] hypereosinophilic syndrome,[134] Kimura's disease,[135,136] eosinophilic pustulosis,[137] metastatic Crohn's disease,[138,139] necrobiosis lipoidica,[140] panniculitis,[141-143] IgA pemphigus,[144] paraneoplastic pemphigus,[145] impetigo herpetiformes,[146] sleromyxedema,[147] and xanthomas.[148]

CONCLUSION

Although moderate to severe psoriasis remains the only FDA-approved indication for the use of cyclosporine in dermatology, the drug has been used with very good results for the treatment of multiple dermatologic conditions, including atopic dermatitis, neutrophilic dermatoses, connective tissue disorders, and autoimmune bullous diseases among others. In our opinion, cyclosporine plays an essential role in the dermatologic therapeutic arsenal due to its efficacy and rapid onset of action. Furthermore, short-term therapy and low doses translate into fewer side effects. It is also important to note that in dermatology, cyclosporine is frequently used as monotherapy and therefore the rates of complication are seen in a small percentage of patients.

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REFERENCES

1. Amor K, Catriona R, et al. The use of cyclosporine in dermatology: Part I. *J Am Acad Dermatol* 2010; 63: 925-46.
2. Mueller W, Hermann B. Cyclosporin A for psoriasis. N Engl J Med 1979;301: 555.
3. Griffiths CEM, Powles AV, Leonard JN, Fry L. Clearance of psoriasis with low dose cyclosporine. *Br Med J* 1986; 293: 731-2.
4. Feutren G, Friend D, Timonen P, Laburte C. Cyclosporin monitoring in psoriasis. *Lancet* 1990;335: 866-7.
5. Timonen P, Friend D, Abeywickrama K, Laburte C, Von Graffenried B, Feutren G. Efficacy of low-dose cyclosporine A in psoriasis: results of dose-finding studies. *Br J Dermatol* 1990;122:33-9.
6. Ellis CN, Fradin MS, Messana JM, Brown MD, Siegel MT, Hartley AH, et al. Cyclosporine for plaque-type psoriasis. Results of a multidose, double-blind trial. *N Engl J Med* 1991; 324:277-84.
7. Christophers E, Mrowietz U, Henneick HH, Fa¨rber L, Welzel D. Cyclosporine in psoriasis: a multicenter dose-finding study in severe plaque psoriaisis. *J Am Acad Dermatol* 1992;26:86-90.
8. Menter A, Korman NJ, Elmets CA, Feldman SR, Gelfand JM, Gordon KB, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis: section 4. Guidelines of care for the management and treatment of psoriasis with traditional systemic agents. *J Am Acad Dermatol* 2009;61:451-85.
9. Ellis CN, Fradin MS, Messana JM et al. Cyclosporine for plaque-type psoriasis. Results of a multidose, double-blind trial. *N Engl J Med* 1991;324: 277–284.
10. Ho VC, Griffiths CE, Berth-Jones J et al. Intermittent short courses of cyclosporine microemulsion for the long-term management of psoriasis: a 2-year cohort study. *J Am Acad Dermatol* 2001; 44: 643–651.
11. Marcil I, Stern RS. Squamous-cell cancer of the skin in patients given PUVA and ciclosporin: nested cohort crossover study. *Lancet* 2001;358: 1042–1045.
12. Paul CF, Ho VC, McGeown C et al. Risk of malignancies in psoriasis treated with cyclosporine: a 5-yr cohort study. *J Invest Dermatol* 2003; 120: 211–6.
13. Lebwohl M, Ellis C, Gottlieb A, Koo J, Krueger G, Linden K, et al. Cyclosporine consensus conference: with emphasis on the treatment of psoriasis. *J Am Acad Dermatol* 1998;39:464-75.
14. Griffiths CE, Katsambas A, Dijkmans BA, Finlay AY, Ho VC, Johnston A, et al. Update on the use of ciclosporin in immune-mediated dermatoses. *Br J Dermatol* 2006;155:1-16.
15. Berth-Jones J, Henderson CA, Munro CS, Rogers S, Chalmers RJG, Boffa MJ, et al. Treatment of psoriasis with intermittent short course cyclosporine (Neoral). A multicenter study. *Br J Dermatol* 1997;136:527-30.
16. Ho VC, Griffiths CE, Albrecht G, Vanaclocha F, Leo´ n-Dorantes G, Atakan N, et al. Intermittent short courses of cyclosporine (Neoral) for psoriasis unresponsive to topical therapy: a 1-year multicentre, randomized study. The PISCES Study Group. *Br J Dermatol* 1999;141:283-91.
17. Ho VC, Griffiths CE, Berth-Jones J, Papp KA, Vanaclocha F, Dauden E, et al. Intermittent short courses of cyclosporine microemulsion for the long-term management of psoriasis: a 2-year cohort study. J Am Acad Dermatol 2001;44:643-51.
18. Pathirana D, Ormerod AD, Saiag P, Smith C, Spuls PI, Nast A, et al. European S3-guidelines on the systemic treatment of psoriasis vulgaris. *J Eur Acad Dermatol Venereol* 2009;23:1-70.
19. Menter MA, See JA, Amend WJ, Ellis CN, Krueger GG, Lebwohl M, et al. Proceedings of the psoriasis combination and rotation therapy conference. Deer Valley, Utah, Oct. 7-9, 1994. *J Am Acad Dermatol* 1996;34:315-21.
20. Griffiths CEM, Powles AV, McFadden J, Baker BS, Valdimarsson H, Fry L. Long term cyclosporine for psoriasis. *Br J Dermatol* 1989;120:256-66.
21. Ozawa A, Sugai J, Ohkido M, Ohtsuki M, Nakagawa H, Kitahara H, et al. Cyclosporin in psoriasis: continuous monotherapy versus intermittent long-term therapy. *Eur J Dermatol* 1999;9:218-23.
22. Grossman RM, Thivolet J, Claudy A, Souteyrand P, Guilhou JJ, Thomas P, et al. A novel therapeutic approach to psoriasis with combination calcipotriol ointment and very low-dose cyclosporine: results of a multicenter placebo-controlled study. *J Am Acad Dermatol* 1994;31:68-74.
23. Gottlieb SL, Heftler NS, Gilleaudeau P, Johnson R, Vallat VP, Wolfe J, et al. Short-contact anthralin treatment augments therapeutic efficacy of cyclosporine in psoriasis: a clinical and pathologic study. *J Am Acad Dermatol* 1995;33:637-45.
24. Abel EA. Phototherapy: Uvb and PUVA. *Cutis* 1999;64:339-42.
25. Korstanje MJ, Hulsmans RF. Combination therapy cyclosporine A-PUVA in psoriasis. *Acta Derm Venereol* 1990;70:89-90.
26. Momtaz TK, Fitzpatrick TB. Modifications of PUVA. Dermatol Clin 1995;13:867-73.
27. van de Kerkhof PC. Therapeutic strategies: rotational therapy and combinations. *Clin Exp Dermatol* 2001;26:356-61.
28. van de Kerkhof PC, de Rooij MJ. Multiple squamous cell carcinomas in a psoriatic patient following high-dose photochemotherapy and cyclosporin treatment: response to long-term acitretin maintenance. *Br J Dermatol* 1997;136:275-8.
29. Fraser AD, van Kuijk AW, Westhovens R, Karim Z, Wakefield R, Gerards AH, et al. A randomized, double blind, placebo controlled, multicenter trial of combination therapy with methotrexate plus cyclosporin in patients with active psoriatic arthritis. *Ann Rheum Dis* 2005;64:859-64.
30. Mazzanti G, Coloni L, De Sabbata G, Paladini G. Methotrexate and cyclosporin combined therapy in severe psoriatic arthritis: a pilot study. *Acta Derm Venereol Suppl (Stockh)* 1994;186:116-7.
31. Aydin F, Canturk T, Senturk N, Turanli AY. Methotrexate and cyclosporin combination for the treatment of severe psoriasis. Clin Exp Dermatol 2006;31:520-4.
32. Wong KC, Georgouras K. Low dose cyclosporin A and methotrexate in the treatment of psoriasis. *Acta Derm Venereo*l 1999;79:87.
33. Gul U, Gonul M, Kilic A, Erdem R, Cakmak SK, Gunduz H. Treatment of psoriatic arthritis with etanercept, methotrexate, and cyclosporin *A. Clin Ther* 2006;28:251-4.
34. Clark CM, Kirby B, Morris AD, Davison S, Zaki I, Emerson R, et al. Combination treatment with methotrexate and cyclosporine for severe recalcitrant psoriasis. *Br J Dermatol* 1999; 141:279-82.
35. Nijsten TE, Stern RS. Oral retinoid use reduces cutaneous squamous cell carcinoma risk in patients with psoriasis treated with psoralen-UVA: a nested cohort study. *J Am Acad Dermatol* 2003; 49: 644–50.
36. Marquez C, Bair SM, Smithberger E, Cherpelis BS, Glass LF. Systemic retinoids for chemoprevention of non-melanoma skin cancer in high-risk patients. *J Drugs Dermatol.* 2010;9(7):753-8.
37. Lebwohl M. Combining the new biologic agents with our current psoriasis armamentarium. *J Am Acad Dermatol* 2003;49(Suppl):S118-24.
38. Cather JC, Menter A. Combining traditional agents and biologics for the treatment of psoriasis. *Semin Cutan Med Surg* 2005;24:37-45.
39. Stebbins WG, Lebwohl MG. Biologics in combination with nonbiologics: efficacy and safety. *Dermatol Ther* 2004;17:432-40.
40. Tuxen AJ, Yong MK, Street AC, Dolianitis C. Disseminated cryptococcal infection in a patient with severe psoriasis treated with efalizumab, methotrexate and cyclosporin. *Br J Dermatol* 2007;157:1067-8.

41. Fraser AD, van Kuijk AW, Westhovens R, Karim Z, Wakefield R, Gerards AH, et al. A randomized, double blind, placebo controlled, multicentre trial of combination therapy with methotrexate plus ciclosporin in patients with active psoriatic arthritis. *Ann Rheum Dis* 2005;64:859-64.
42. Mahrle G, Schulze HJ, Bra¨utigam M, Mischer P, Schopf R, Jung EG, et al. Anti-inflammatory efficacy of low-dose cyclosporine A in psoriatic arthritis. A prospective multicentre study. *Br J Dermatol* 1996;135:752-7.
43. Laburte C, Grossman R, Abi-Rached J et al. Efficacy and safety of oral cyclosporin A (CyA; Sandimmun) for long-term treatment of chronic severe plaque psoriasis. *Br J Dermatol* 1994; 130:366–375.
44. Paul CF, et al. Risk of malignancies in psoriasis patients treated with cyclosporine: a 5 year cohort study. *J Invest Dermatol.* 2003; 120(2):211-16.
45. Shin Woo, Young Woon, et al. Cyclosporine treatment of Atopic Dermatitis: It is really associated with infectious diseases? *Ann Dermatol* 2010;22(2): 170-172.
46. Toyoda M, Morohashi M. Morphological assessment of the effects of cyclosporine A on Mast Cell- Nerve relationship in Atopic Dermatitis. *Acta Derm Venereol (Stochkh)* 1998;78: 321-325.
47. Th. Van J, Heule F et al. Cyclosporine in atopic dermatitis. *Br J Dermatol.* 1994; 130:634-640.
48. Haw S, Shin MK et al. The efficacy and Safety of Long-term Oral Cyclosporine treatment for patients with Atopic Dermatitis. *Ann Dermatol.* 2010;22(1):9-15.
49. Frankel HC, Frangos JE et al. Tapering cyclosporine after long term treatment for atopic dermatitis. J of Eur Acad Dermatol and Venereol. 2011. Jun 4.
50. Ohtsuka Tsutomu. Response to oral cyclosporine therapy and high sensitivity-CRP level in chronic idiopathic urticaria. Int J Dermatol 2010;49:579-584.
51. Kessel A. Toubi E. Cyclosporine-A in severe chronic urticaria: the option for long-term therapy. *Allergy* 2010;65:1478-1482.
52. Hye YJ, Hei SK, et al. Cyclosporine treatment in a patient with concurrrent Autoimmune urticaria and Autoimmune Hepatitis. *Ann Dermatol* 2009; 21(3):291-293.
53. Bertha-Jones J, Smith S G et al. Nodular prurigo responds to cyclosporine. *Br J Dermatol* 1995;132:795-799.
54. Wallengren J. Prurigo: diagnosis and management. Am J Clin Dermatol 2004;5 (2):85-95.
55. Lee. M, Shumack S. Prurigo Nodularis: A review. *Australasian Journal of Dermatol* 2005; 46:211-220.
56. Elgart G, Stover P, Larson K, Sutter C,et al. Treatment of pyoderma gangrenosum with cyclosporine: results in seven patients. *J Am Acad Dermatol.* 1991;24(1):83-6.
57. Hasselmann DO, Bens G, Tilgen W, Reichrath J. Pyoderma gangrenosum: clinical presentation and outcome in 18 cases and review of the literature. *J Dtsch Dermatol Ges* 2007;5:560-4
58. Reich A, Maj J, Cisło M, Szepietowski JC. Periungual lesions in pyoderma gangrenosum. *Clin Exp Dermatol* 2009;34(5):e81-4.
59. Reichrath J, Bens G, Bonowitz A, Tilgen W, Treatment recommendations for pyoderma gangrenosum: an evidence based review of the literature based on more than 350 patients. *J Am Acad Dermatol* 2005;53:273-83.
60. Soria C, Allegue F, Martin M, Ledo A. Treatment of pyoderma gangrenosum with cyclosporine A. *Clinical and experimental Dermatology.*1991 Sep;16(5):392-394.
61. Turner RB, Emer JJ, Weill M, et al. Rapid resolution of pyoderma gangrenosum after treatment with intravenous cyclosporine. *J Am Acad Dermatol.* 2010;63(3):e72-4
62. Friedman S, Marion JF, Scherl E, Rubin PH, Present DH. Intravenous cyclosporine in refractory pyoderma gangrenosum complicating inflammatory bowel disease. *Inflamm Bowel Dis* 2001;7:1-7
63. Azizan NZ, Gangaram HB, Hussein SH. A novel therapy for the treatment of pyoderma gangrenosum. *Med J Malaysia* 2008 Mar;63(1):51-4
64. Wenzel J, Gerdsen R, Phillipp-Dormston W, et al.Topical treatment of pyoderma gangrenosum. *Dermatology* 2002;205(3):221-3
65. Feliciani C, Tulli A. Topical cyclosporine in the treatment of dermatology diseases. *Int J Immunopathol Pharmacol.* 2002;15(2):89-93
66. Cohen PR. Neutrophilic Dermatoses : a review of the current treatment options. *Am J Clin Dermato*l 2009;10 (5):301-12.
67. Wilson DM, John GR, Callen JP. Peripheral ulcerative keratitis, an extracutaneous neutrophilic disorder: report of a patient with rheumathoid arthritis, pustular vasculitis, pyoderma gangrenosusm and Sweet's syndrome with an excellent response to cyclosporine treatment. *J Am Acad Dermatol.*1999;40:331-4
68. Von Den Driesch P. Sweet's syndrome (acute febrile neutrophilic dermatosis) *J Am Acad Dermatol* 1994;314:535-56.
69. Von Den Driesch P. Sweet's syndrome-Therapy with cyclosporin. *Clin Experimental Dermatol* 1994; 19(3):274-7
70. Bourke JF, Bertha-Jones J, Graham-Brown RA. Sweet's syndrome responding to Cyclosporin. *Br J Dermatol.*1992; 127(1):36-8
71. Fabbri P, Cardinali C, Giomi B, Caproni M. Cutaneous lupus erythematosus: diagnosis and management. *Am J Clin Dermatol.* 2003;4:449-65.
72. Panjwani S. Early diagnosis and treatment of discoid lupus erythematosus. *J Am Board Fam Med.* 2009;22:206-13.
73. Rothe MJ, Kerdel FA. Treatment of cutaneous lupus erythematosus. *Lupus.* 1992;1:351-6.
74. Ogawa H, Kameda H, Amano K, Takeuchi T. Efficacy and safety of cyclosporine A in patients with refractory systemic lupus erythematosus in a daily clinical practice. *Lupus.* 2010;19:162-9.
75. Klein A, Vogt T, Wenzel SM, Fleck M, Landthaler M. Cyclosporin combined with methotrexate in two patients with recalcitrant subacute cutaneous lupus erythematosus. *Australas J Dermatol.* 2011;52:43-7.
76. Grabbe S, Kolde G. Coexisting lichen planus and subacute cutaneous lupus erythematosus. *Clin Exp Dermatol.* 1995;20:249-54.
77. Kontochristopoulos GJ, Giannadaki M, Doulaveri G, Christofidou E, Zakopoulou N. Psoriasis coexisting with subacute cutaneous lupus erythematosus. *J Eur Acad Dermatol Venereol.* 2004;18:385-6.
78. Gruson LM, Cohen DE. Dermatomyositis. Dermatol Online J. 2004;10:7.
79. Rosa Neto NS, Goldenstein-Schainberg C. Juvenile dermatomyositis: review and update of the pathogenesis and treatment. *Rev Bras Reumatol.* 2010;50(3):299-312.
80. Arnson Y, Dovrish Z, Hadari R, Amital H. Amyopathic dermatomyositis–an uncommon presentation of dermatomyositis. *Isr Med Assoc J.* 2007;9:492-3.
81. 81. Ytterberg SR. Treatment of refractory polymyositis and dermatomyositis. *Curr Rheumatol Rep.* 2006;8:167-73.
82. Amor KT, Ryan C, Menter A. The use of cyclosporine in dermatology: part I. *J Am Acad Dermatol.* 2010;63:925-46.
83. Iorizzo LJ 3rd, Jorizzo JL. The treatment and prognosis of dermatomyositis: an updated review. *J Am Acad Dermatol.* 2008;59:99-112.
84. Vencovský J, Jarosová K, Machácek S, Studýnková J, Kafková J, Bartůnková J, Nemcová D, Charvát F. Cyclosporine A versus methotrexate in the treatment of polymyositis and dermatomyositis. *Scand J Rheumatol.* 2000;29:95-102.
85. Miyake S, Ohtani Y, Sawada M, Inase N, Miyazaki Y, Takano S, Miyasaka N, Yoshizawa Y. Usefulness of cyclosporine A on rapidly progressive interstitial pneumonia in dermatomyositis. *Sarcoidosis Vasc Diffuse Lung Dis.* 2002;19:128-33.
86. Mii S, Niiyama S, Kusunoki M, Arai S, Katsuoka K. Cyclosporine A as treatment of esophageal involvement in dermatomyositis. *Rheumatol Int.* 2006;27:183-5.
87. Shimojima Y, Ishii W, Kato T, Hoshi K, Matsuda M, Hashimoto T, Tanaka Y, Ikeda S. Intractable skin necrosis and interstitial pneumonia in amyopathic dermatomyositis, successfully treated with cyclosporin *A. Intern Med.* 2003;42:1253-8.
88. Alkhalifah A, Alsantali A, Wang E, McElwee KJ, Shapiro J. Alopecia areata update: part II. Treatment. *J Am Acad Dermatol.* 2010;62:191-202.
89. Ito T, Aoshima M, Ito N, Uchiyama I, Sakamoto K, Kawamura T, Yagi H, Hashizume H, Takigawa M. Combination therapy with oral PUVA and corticosteroid for recalcitrant alopecia areata. *Arch Dermatol Res.* 2009;301:373-80.
90. Shaheedi-Dadras M, Karami A, Mollaei F, Moravvej H, Malekzad F. The effect of methylprednisolone pulse-therapy plus oral cyclosporine in the treatment of alopecia totalis and universalis. Arch Iran Med. 2008;11:90-3. Erratum in: *Arch Iran Med.* 2008 Mar;11(2):241.
91. Kim BJ, Min SU, Park KY, Choi JW, Park SW, Youn SW, Park KC, Huh CH. Combination therapy of cyclosporine and methylprednisolone on severe alopecia areata. *J Dermatolog Treat.* 2008;19:216-20.
92. Alpsoy E, Akman A. Behçet's disease: an algorithmic approach to its treatment. *Arch Dermatol Res.* 2009;301:693-702.
93. Mendes D, Correia M, Barbedo M, Vaio T, Mota M, Gonçalves O, Valente J.Behçet's disease--a contemporary review. *J Autoimmun.* 200;32:178-88.
94. Hatemi G, Silman A, Bang D, Bodaghi B, Chamberlain AM, Gul A, Houman MH, Kötter I, Olivieri I, Salvarani C, Sfikakis PP, Siva A, Stanford MR, Stübiger N, Yurdakul S, Yazici H; EULAR Expert Committee. EULAR recommendations for the management of Behçet disease. *Ann Rheum Dis.* 2008;67:1656-62.
95. Lin P, Liang G. Behçet disease: recommendation for clinical management of mucocutaneous lesions. *J Clin Rheumatol.* 2006 ;12:282-6.
96. Evereklioglu C. Current concepts in the etiology and treatment of Behçet disease. *Surv Ophthalmol.* 2005;50:297-350.
97. Spadino S, Altomare A, Cainelli C, Franchi C, Frigerio E, Garutti C, Taglioni M, Altomare GF. Disseminated granuloma annulare: efficacy of cyclosporine therapy. *Int J Immunopathol Pharmacol.* 2006;19:433-8.
98. Bischoff L, Derk CT. Eosinophilic fasciitis: demographics, disease pattern and response to treatment: report of 12 cases and review of the literature. *Int J Dermatol.* 2008;47:29-35.
99. Antic M, Lautenschlager S, Itin PH. Eosinophilic fasciitis 30 years after -what do we really know? Report of 11 patients and review of the literature. *Dermatology.* 2006;213(2):93-101.
100. Valencia IC, Chang A, Kirsner RS, Kerdel FA. Eosinophilic fasciitis responsive to treatment with pulsed steroids and cyclosporine. *Int J Dermatol.* 1999 May;38:369-72.
101. Bukiej A, Dropiński J, Dyduch G, Szczeklik A. Eosinophilic fasciitis successfully treated with cyclosporine. *Clin Rheumatol.* 2005;24:634-6.
102. Tămaş MM, Baican C, Rednic S. Hyperimmunoglobulin E syndrome (Job's syndrome). *Rom J Intern Med.* 2008;46:169-71.

103. DeWitt CA, Bishop AB, Buescher LS, Stone SP. Hyperimmunoglobulin E syndrome: two cases and a review of the literature. *J Am Acad Dermatol.* 2006;54:855-65.
104. Wolach B, Eliakim A, Pomeranz A, Cohen AH, Nusbacher J, Metzker A. Cyclosporin treatment of hyperimmunoglobulin E syndrome. *Lancet* 1996;347:67.
105. Schepis C, Lentini M, Siragusa M. Erosive lichen planus on an atypical site mimicking a factitial dermatitis. *Acta Derm Venereol.* 2010;90:185-6.
106. Schepis C, Siragusa M, Lentini M. Erosive lichen planus: two uncommon cases. *Acta Derm Venereol.* 2008;88:268-70.
107. Ismail SB, Kumar SK, Zain RB. Oral lichen planus and lichenoid reactions: etiopathogenesis, diagnosis, management and malignant transformation. *J Oral Sci.* 2007 Jun;49(2):89-106. Review. PubMed PMID: 17634721.
108. Mirmirani P, Willey A, Price VH. Short course of oral cyclosporine in lichen planopilaris. *J Am Acad Dermatol.* 2003;49:667-71.
109. Lane TK, Kamino H, Walters RF, Meehan S, Pomeranz MK. Lichen planopilaris and psoriasis. *Dermatol Online J.* 2008;14:4.
110. Bulbul Baskan E, Turan H, Tunali S, Toker SC, Saricaoglu H. Open-label trial of cyclosporine for vulvar lichen sclerosus. *J Am Acad Dermatol.* 2007;57:276-8.
111. Schiavo AL, Puca RV, Ruocco V, Ruocco E. Adjuvant drugs in autoimmune bullous iseases, efficacy versus safety: Facts and controversies. *Clin Dermatol.* 2010;28:337-43.
112. Olszewska M, Kolacinska-Strasz Z, Sulej J, Labecka H, Cwikla J, Natorska U, Blaszczyk M. Efficacy and safety of cyclophosphamide, azathioprine, and cyclosporine (ciclosporin) as adjuvant drugs in pemphigus vulgaris. *Am J Clin Dermatol.* 2007;8:85-92.
113. Tirado-Sánchez A, León-Dorantes G. Treatment of pemphigus vulgaris. An overview in Mexico. *Allergol Immunopathol (Madr).* 2006 Jan;34:10-6.
114. Chrysomallis F, Ioannides D, Teknetzis A, Panagiotidou D, Minas A. Treatment of oral pemphigus vulgaris. *Int J Dermatol.* 1994;33:803-7.
115. Alsaleh QA, Nanda A, Al-Baghli NM, Dvorak R. Pemphigus in Kuwait. *Int J Dermatol.* 1999;38:351-6.
116. Martin LK, Werth V, Villanueva E, Segall J, Murrell DF. Interventions for pemphigus vulgaris and pemphigus foliaceus. *Cochrane Database Syst Rev.* 2009 Jan 21;(1):CD006263.
117. 117. Millard TP, Hawk JL. Photosensitivity disorders: cause, effect and management. *Am J Clin Dermatol.* 2002;3:239-46.
118. 118. Stinco G, Codutti R, Frattasio A, De Francesco V, Patrone P. Chronic actinic dermatitis treated with cyclosporine-A. Eur J Dermatol. 2002;12:455-7.
119. Booth AV, Ma L. Pityriasis rubra pilaris, type 1. *Dermatol Online J.* 2005;11:9.
120. Usuki K, Sekiyama M, Shimada T, Shimada S, Kanzaki T. Three cases of pityriasis rubra pilaris successfully treated with cyclosporin A. *Dermatology.* 2000;200:324-7.
121. Manno R, Boin F. Immunotherapy of systemic sclerosis. *Immunotherapy.* 2010;2:863-78.
122. Ippoliti G, Miori L, Negri M, Rovati B, Lorenzutti F, Zerbinati N, Rabbiosi G. Cyclosporine in treatment of progressive systemic sclerosis: clinical and immunologic findings. *Transplant Proc.* 1994;26:3117-8.
123. Morton SJ, Powell RJ. Cyclosporin and tacrolimus: their use in a routine clinical setting for scleroderma. *Rheumatology (Oxford).* 2000;39:865-9.
124. Worswick S, Cotliar J. Stevens-Johnson syndrome and toxic epidermal necrolysis: a review of treatment options. *Dermatol Ther.* 2011;24:207-18.
125. Kumari R, Timshina DK, Thappa DM. Drug hypersensitivity syndrome. Indian *J Dermatol Venereol Leprol.* 2011;77:7-15.
126. Rajaratnam R, Mann C, Balasubramaniam P, Marsden JR, Taibjee SM, Shah F, Lim R, Papini R, Moiemen N, Lewis H. Toxic epidermal necrolysis: retrospective analysis of 21 consecutive cases managed at a tertiary centre. *Clin Exp Dermatol.*2010;35:853-62.
127. Paquet P, Piérard GE. New insights in toxic epidermal necrolysis (Lyell's syndrome): clinical considerations, pathobiology and targeted treatments revisited. *Drug Saf.* 2010;33:189-212.
128. Khalili B, Bahna SL. Pathogenesis and recent therapeutic trends in Stevens-Johnson syndrome and toxic epidermal necrolysis. *Ann Allergy Asthma Immunol.* 2006;97:272-80.
129. Matsushita K, Ozaki A, Inoue H, Kaieda T, Akimoto M, Satomura A, Arima N, Hamada H, Suruga Y, Aoki N, Fujiwara H, Tei C. Stevens-Johnson syndrome induced by mizoribine in a patient with systemic lupus erythematosus. *Mod Rheumatol.* 2006;16:113-6.
130. Peru H, Soylemezoglu O, Bakkaloglu SA, Elmas S, Bozkaya D, Elmaci AM, Kara F, Buyan N, Hasanoglu E. Henoch Schonlein purpura in childhood: clinical analysis of 254 cases over a 3-year period. *Clin Rheumatol.* 2008;27:1087-92.
131. Carlson JA, Cavaliere LF, Grant-Kels JM. Cutaneous vasculitis: diagnosis and management. *Clin Dermatol.* 2006;24:414-29.
132. Venzor J, Lee WL, Huston DP. Urticarial vasculitis. *Clin Rev Allergy Immunol.* 2002;23:201-16.
133. Tsutsui K, Hirone T, Kubo K, Matsui Y. Annular elastolytic giant cell granuloma: response to cyclosporin A. *J Dermatol. 1*994;21:426-9.
134. Hayashi M, Kawaguchi M, Mitsuhashi Y, Suzuki T. Case of hypereosinophilic syndrome with cutaneous necrotizing vasculitis. *J Dermatol.* 2008;35:229-33.
135. Shenoy VV, Joshi SR, Kotwal VS, Shedge RT, Ramraje NN, Lanjewar DN. Recurrent Kimura's disease: excellent response to cyclosporine. *J Assoc Physicians India.* 2006;54:153-5.
136. Birol A, Bozdogan O, Keleş H, Kazkayasi M, Bagci Y, Kara S, Koçak M, Birol A. Kimura's disease in a Caucasian male treated with cyclosporine. *Int J Dermatol.* 2005;44:1059-60.
137. Sugita K, Kabashima K, Koga C, Tokura Y. Eosinophilic pustular folliculitis successfully treated with sequential therapy of interferon-gamma and ciclosporin. *Clin Exp Dermatol.* 2006 Sep;31:709-10.
138. Palamaras I, El-Jabbour J, Pietropaolo N, Thomson P, Mann S, Robles W, Stevens HP. Metastatic Crohn's disease: a review. *J Eur Acad Dermatol Venereol.* 2008;22:1033-43.
139. Carranza DC, Young L. Successful treatment of metastatic Crohn's disease with cyclosporine. *J Drugs Dermatol.* 2008;7:789-91.
140. Stanway A, Rademaker M, Newman P. Healing of severe ulcerative necrobiosis lipoidica with cyclosporin. Australas J Dermatol. 2004;45:119-22.
141. Migliore A, Bizzi E, Santacroce CM, Tarquini E, Massafra U, Vacca F, Martin Martin LS. Mixed panniculitis responding to cyclosporin-A with a 12-month follow-up: a case report. *Int J Immunopathol Pharmacol.* 2009;22:1143-6.
142. Rojnuckarin P, Nakorn TN, Assanasen T, Wannakrairot P, Intragumtornchai T. Cyclosporin in subcutaneous panniculitis-like T-cell lymphoma. *Leuk Lymphoma.* 2007;48:560-3.
143. Al Zolibani AA, Al Robaee AA, Qureshi MG, Al Nosian H. Subcutaneous panniculitis-like T-cell lymphoma with hemophagocytic syndrome successfully treated with cyclosporin A. *Skinmed.* 2006;5:195-7.
144. Tajima M, Mitsuhashi Y, Irisawa R, Amagai M, Hashimoto T, Tsuboi R. IgA pemphigus reacting exclusively to desmoglein 3. Eur J Dermatol. 2010;20:626-9. Erratum in: *Eur J Dermatol.* 2011;21:152.
145. Gergely L, Váróczy L, Vadász G, Remenyik E, Illés A. Successful treatment of B cell chronic lymphocytic leukemia-associated severe paraneoplastic pemphigus with cyclosporin A. *Acta Haematol.* 2003;109:202-5.
146. Valdés E, Núñez T, Pedraza D, Muñoz H. Recurrent Impetigo Herpetiformis: successfully managed with ciclosporine. Report of one case. *Rev Med Chil.* 2005;133:1070-4.
147. Bata-Csorgo Z, Husz S, Foldes M, Korom I, Molnar K, Morvay M, Dobozy A. Scleromyxedema. *J Am Acad Dermatol.* 1999;41(2 Pt 2):343-6.
148. Saigoh S, Tashiro A, Fujita S, Matsui M, Shibata S, Takeshita H, Duan H, Moroi Y, Urabe K, Koga T, Furue M. Successful treatment of intractable scleromyxedema with cyclosporin A. *Dermatology.* 2003;207:410-1.
149. Nakajima K, Ikeda M, Nakajima H, Kodama H. Regression of secondary plane xanthomas using cyclosporine A. *Int J Dermatol.* 2006;45:1136-8.

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