Current Best Evidence

Current best evidence from dermatology literature

Altaei T. The treatment of melasma by silymarin cream. BMC Dermatol 2012;12:18.

Melasma is an acquired increased pigmentation of the skin characterized by symmetrical and confluent grey-brown patches on the face. The etiology is not entirely elucidated. The study was carried out to assess the safety and efficacy of topical Silymarin (SM) cream in a double-blind (DB) placebo controlled fashion for treatment of melasma patients.

Experimentally, 24 Albino rabbits were randomly divided into four equal groups. (A) No treatment, (B) received placebo, (C) treated with SM cream (0.1 mg/ml/kg), and (D) treated by SM (0.2 mg/ml/kg), applied topically 30 min before Ultraviolet (UV) sunlight exposure for 3 h daily for 30 days were assessed clinically and by tissue pathology. Clinically, on 96 adults diagnosed with melasma randomized to three equal groups: Group I (G I) SM (7 mg/ml) cream, Group II (G II) SM (14 mg/ml) cream or Group III placebo, applied topically to the affected areas, twice daily for 4 weeks to receive one of the tested drugs applied twice daily for 4 weeks, evaluated by the response; lesion size, melasma area and severity index score (MASI), Physician global assessment (PGA), and subjective assessment.

Eighty were females and sixteen were males, aged between 28 years and 55 years, duration varied from 2 years to 6 years. Frequent precipitating factor was the sun exposure (90%). Clinically; all patients had excellent improvement and lesion size reduction with SM treatment from the 1st week. The average change in MASI score and improvement graded by PGA of G I and G II before and after treatment was statistically significant compared to the placebo group. No local or systemic adverse effects were noted.

Comment: UV irradiation present in sunlight is like a double edged sword with both beneficial and detrimental effects. Melasma predominantly affects sun-exposed areas, common in women. The pathogenesis of melasma is not fully understood; UV exposure, genetic influences, and hormonal changes being the most commonly cited etiologic factors. Recently, it has been demonstrated that the generation of oxygen free radicals in response to the UV light is involved in the pathogenesis of melasma. Although many agents are available in the therapeutic armamentarium of melasma, its management is still challenging.

A lot of interest has been generated in plant-derived products for their antioxidant activity. Effective botanical antioxidant compounds are widely used in traditional medicine and include tocopherols, flavonoids, phenolic acids, nitrogen containing compounds (indoles, alkaloids, amines, and amino acids), and monoterpenes. Human studies have convincingly demonstrated pronounced photoprotective effects of natural and synthetic antioxidants when applied topically before ultraviolet rays (UVR) exposure. Particularly with respect to ultraviolet B (UVB) induced skin damage like erythema, the photoprotective effects of antioxidants are significant when applied in distinct mixtures in appropriate vehicles. Furthermore, sunscreens may also benefit from the combination with antioxidants resulting in increased safety and efficacy. SM is derived from the milk of the thistle plant and is a natural polyphenolic flavinoid. Silibinin (silybin) is its major active constituent hence considered to be the most biologically active and potent antioxidant and significantly prevents melanin production.

More studies are required to prove this preliminary report showing the efficacy of SM in (melasma); thus, opening a new therapeutic window in the treatment of this simple, but agonizing disorder of hyperpigmentation.

Haushalter K, Murad EJ, Dabade TS, Rowell R, Pearce DJ, Feldman SR. Efficacy of low-dose acitretin in the treatment of psoriasis. J Dermatolog Treat 2012;23:400-3.

Acitretin is the only oral retinoid currently approved

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by the US Food and Drug Administration for the treatment of severe psoriasis. The original acitretin pivotal trials consisted of a DB treatment period of 8 weeks from which, acitretin was approved at doses of 25-50 mg/day. Subsequent clinical experience suggests that low doses of acitretin (i.e., 25 mg/day) may provide effcacy while minimizing adverse events. The 8-week data from the original trials may have underestimated the efficacy of acitretin when used at lower doses over longer periods.

In the present study, the acitretin pivotal trials for acitretin are revisited; taking into consideration the original 8-week data, taken together with the results of a subsequent 24-week open label (OL) phase. The goal of this retrospective analysis is to determine the efficacy of low-dose acitretin (25 mg/day) over a time frame that is more relevant to the real world treatment of psoriasis.

Trial A (n = 171) compared two dosages of acitretin (25 and 50 mg/day) with placebo, while Trial B (n = 333) compared four dosages of acitretin (10, 25, 50, and 75 mg/day) with placebo. Both trials consisted of two phases: 8 weeks of placebo-controlled, DB treatment immediately followed by 16 weeks of OL use. End points for efficacy like the reduction in body surface area (BSA) and success of treatment as determined by 7-point Investigator Static Global Assessment (ISGA), were assessed at 2, 4, 6, and 8 weeks. During the double-blind (DB) phase, low-dose acitretin was defined as 25 mg/day and high dose treatment was defined as 50 mg/day. The doses were titrated up or down as needed during the OL phase, low- and high-dose treatment groups were defined based on mean daily dose, with average doses <30 mg/day defined as low-dose and average doses >30 mg/day defined as high-dose.

These definitions yielded group-wide average doses of 22.2-24.4 mg/day for the OL low-dose groups (L to L and H to L) and 50.0-52.4 mg/day for the high-dose OL groups (H to H and L to H). The data from Trials A and B were combined, and two separate analyses were performed. In Analysis 1, patients were divided into four groups, (1) High-dose DB to Low-dose OL (H to L), n = 23 (2) High-dose DB to High-dose OL (H to H), n = 77 (3) Low-dose DB to Low-dose OL (L to L), n = 19 (4) Low-dose DB to High-dose OL (L to H), n = 52. Analysis two was conducted by grouping patients according to the dose of acitretin received during the 8-week DB phase only, regardless of the dose eventually used during the OL extension-five groups being: Placebo (n = 101), 10 mg/day (n = 28), 25 mg/day (n = 75), 50 mg/day (n = 101), and 75 mg/day (n = 28) out of which placebo, 10, 25, and 50 mg/day were included in the present analysis.

In Analysis 1, rates of treatment success determined by ISGA at the end of 24 weeks were remarkably similar (29-33%), with the exception of L to L group exhibiting a substantially higher treatment success rate of 47%. Percentage reduction of BSA involvement varied more widely among the four groups, although the best result was seen in the L to L group (73.2%).

In Analysis 2, the rates of treatment success and BSA reduction achieved after 24 weeks of treatment were similar among all four groups. The groups receiving 10 or 25 mg doses during the DB phase achieved slightly higher rates of treatment success based on ISGA than the 50 mg group at the end of the OL phase, although overall reduction in the percentage of BSA affected was greater in the 50 mg DB dosing group.

Comment: Acitretin is the pharmacologically active metabolite of etretinate, which it replaced due to its more favorable pharmacokinetic profile. It is an established systemic second-line therapy for severe psoriasis resistant to topical therapy. Apart from chronic plaque psoriasis, acitretin has been reported to be effective in erythrodermic, pustular, and nail psoriasis also.

A number of adverse effects associated with acitretin therapy are dose dependent, thereby limiting the usefulness of this useful drug. Multiple studies in the past have shown that common adverse events are more frequent in patients receiving 50 mg daily compared with patients receiving 25 mg daily. It is thus justified in speculating that by reducing the adverse events and thereby the risk of discontinuation, low-dose of acitretin may result in better long-term effectiveness compared to results with higher doses. Some studies have shown lower doses of 10-25 mg daily of acitretin to be significantly not better than placebo while others have shown discordant results. The study period was however shorter in these studies, which are likely to underestimate the efficacy of acitretin as optimal response is seen after 12 weeks. Taken together, longer-term open extensions with variable doses titrated to the patients' needs suggest greater efficacy over time

as demonstrated in the present study.

However, this analysis could not provide efficacy information with regards to different subtypes of psoriasis as pustular psoriasis may respond less favorably to lower doses of acitretin than psoriasis vulgaris.

Barikbin B, Saadat N, Akbari Z, Yousefi M, Toossi P. Focal high-concentration trichloroacetic acid peeling for treatment of atrophic facial chickenpox scar: An open-label study. Dermatol Surg 2012;38:1662-7.

Chickenpox is a common viral dermatologic disease that leads to persistent facial scars in approximately 7-18% of cases. Patients with facial scars often face esthetic, physical, psychological, and social consequences. Despite their prevalence, there is a paucity of information in the medical literature on the treatment of atrophic chickenpox scars. This article focuses on the efficacy and safety of using the chemical reconstruction of skin scar technique for the treatment of atrophic facial chickenpox scars. The high-risk of adverse events has limited the use of more-invasive modalities such as extensive deep chemical peel, whereas low rates of patient satisfaction have been observed with punch elevation. The cross technique appears to be an effective method for treatment of depressed chickenpox scars.

A total of 100 consecutive subjects with moderate to severe atrophic facial chickenpox scars (<1 cm 2) and Fitzpatrick skin types II to IV were enrolled. Patients were treated with focal chemical peeling with 70% trichloroacetic acid (TCA) repeated at 3-week intervals for a maximum of six sessions. The changes in atrophic scars were scored on an arbitrary scale as follows: Worsening, no change, mild improvement (1-25%), moderate improvement (25-75%), and marked improvement (>75%). Patient satisfaction and adverse events such as erythema, pigmentary changes, herpes simplex flare-up, milia, and scar and keloid formation were also assessed.

Final assessment at 12-week follow-up visit after the last treatment revealed improvement in 95% of patients with mild improvement in 12 cases, moderate improvement in 42 cases, and marked improvement in 41 cases. A total of 79 patients expressed moderate to high satisfaction with the results. Adverse events were noticed in 34 patients with mild erythema in 17 patients, hypopigmentation in 2 patients, and hyperpigmentation in 15 patients, all of which resolved gradually within the study period.

Comment: Chickenpox is a common contagious viral infection that can infrequently result in scars, which are often persistent. The scars can occur on any part of the body, commonly found on the face. They can be hyperpigmented, hypopigmented, atrophic, hypertrophic, sometimes resembling scarring due to variola. Scars on the face can result in lowered self-esteem and self-confidence and social withdrawal. The treatment options available include chemical peeling, dermabrasion, punch excision, punch grafting, fillers, subcision with/without suction, and resurfacing lasers. Cross has been used successfully as a modality for "Focal Acne Scar Treatment" or "F.A.S.T." to treat acne scars, especially the ice-pick scars. However, there is a paucity of information regarding the treatment of chickenpox scars with CROSS technique.

Focal high concentration of TCA can be used to treat the atrophic type of chickenpox scars. In this OL study, improvement was noticed from the third session of treatment in a subset of patients and the rate of improvement was maximum at 12 week follow-up after the treatment. Additional advantage with focal TCA application is the cost-effectiveness of the procedure. Furthermore, it is an office procedure not requiring more than a few minutes. Comparison with other modalities and a control group would provide a better feed through and a fairer idea of the efficacy.

Lowenstein EB, Zeichner JA. Intralesional adalimumab for the treatment of refractory balanitis xerotica obliterans. JAMA Dermatol 2013;149:23-4.

Balanitis xerotica obliterans (BXO) is a form of lichen sclerosus (LS) that affects the penis and can lead to significant morbidity because of scarring and urinary and sexual discomfort. The treatment of BXO is difficult as no single therapy has emerged to be consistently effective. Prevention of significant scarring is the goal of therapy because it leads to psychosocial, sexual, and physical morbidity.

A 60-year-old circumcized man presented with an 8-month history of a gradually worsening painful lesion on his penis with significant erythema, erosions, crusting, and atrophic scarring on the shaft and coronal sulcus. Biopsy was consistent with BXO. He had previously been treated for several months with clobetasol and tacrolimus ointments. The patient was treated with 40 mg of intralesional adalimumab every other week given into

the middle dermis at 1-cm intervals circumferentially around the penile shaft. A dramatic improvement was observed at 2 weeks after the first injections. The improvement continued, and at week 4, the patient's disease was nearly clear. The patient returned for biweekly injections for first 3 months and lesions was cleared for 8 months. Later, the disease relapsed after he waited 10 weeks for treatment. He resumed biweekly intralesional adalimumab injections at month 11, with similar improvement noted once again.

To date, there are little to no data on safety, systemic absorption, dosing regimens or monitoring guidelines for intralesional Tumor necrosis factor (TNF) therapy. Furthermore, intralesional adalimumab therapy is more painful and more costlier than most other modalities, but nonetheless, may represent an option in severe refractory cases. The dramatic response to intralesional adalimumab in this case suggests that local blockade of TNF may be a promising therapy for this frequently recalcitrant and debilitating disease.

Comment: BXO is now considered to be the male genital variant of LS. The clinical presentation and severity of BXO can vary markedly. It was regarded earlier to be occurring exclusively in adults, but currently, it is recognized to be a common cause of acquired phimosis and metal stenosis in children. The presenting complaint is usually tightening of the foreskin, which may lead to phimosis, painful erections and psychosexual problems. The cutaneous lesions of LS are resistant to most topical therapies. Use of corticosteroids and topical calcineurin inhibitors demonstrated modest improvement only. LS shows increased staining for interferon (IFN)-γ, Tumor necrosis factor (TNF)-α, interleukin-1(IL-1) α, IFN-γ receptor, CD25, CD11a and intercellular adhesion molecules (ICAM)-1; hence, forming the basis for treatment with anti-TNF therapy.

Adalimumab is a fully human, anti-tumor necrosis factor alpha monoclonal antibody administered subcutaneously. Intralesional Adalimumab has been tried in necrobiosis lipoidica and cutaneous sarcoidosis. There are little to no data on safety, systemic absorption, dosing regimens or monitoring guidelines for intralesional TNF therapy.

Association between BXO and squamous cell carcinoma (SCC) of the glans has been reported, although by what mechanism this occurs and whether this is a specific causal relationship remains unclear. Malignancy potential of Adalimumab should not be overlooked in the background of BXO. The dramatic response to intralesional adalimumab in the patient may suggest that local blockade of TNF may be a promising therapy for a disease, which is recalcitrant to other treatment modalities. In view of this case report, we need to try this drug in a larger number of patients to substantiate the findings.

Dlova N, Goh CL, Tosti A. Familial frontal fibrosing alopecia. Br J Dermatol 2013;168:220-2.

Frontal fibrosing alopecia (FFA) is a cicatricial alopecia initially described by Kossard in 1994. It primarily affects Caucasian postmenopausal women with progressive recession of the frontotemporal hairline. Most authors consider FFA a variant of lichen planopilaris because of its similar pathological features.

The diagnosis was confirmed in all the 10 patients by pathological examination. Dermoscopy was utilized to select the biopsy site in seven patients. Biopsies were taken from the frontal hairline in areas showing perifollicular erythema and/or scaling. A biopsy from the forearms was also taken in the two Hispanic sisters. Horizontal sections of 4-mm scalp biopsies showed reduced follicular density, a lichenoid lymphocytic infiltrate involving the outer root sheaths of the upper follicles, mild perifollicular fibrosis and follicular drop out.

In three of the four families, FFA occurred in siblings. Affected members of the families either lived together or close by in the same town. In all the families, the diagnosis of FFA was first made on one female patient who then diagnosed and referred her relatives. One of the families consisted of two sisters who developed the disease in their twenties. Both had a history of normal menses and blood tests showed a normal hormonal profile. In another family, FFA affected a brother and a sister which is peculiar as the condition is extremely rare in men. Two families had three affected members, including a black family from South Africa, from where the disease has never been reported.

Comment: FFA is a variety of cicatricial alopecia characterized by fronto-temporal hairline recession with/without a marked decrease or a complete loss of the eyebrows. It is typically observed in women who are

post-menopausal. In the study, none of the 10 patients had involvement of the eyebrows.

FFA is considered by most of the authors to be a variant of lichen planopilaris with selective involvement of certain androgen-dependent areas. The histological findings are indistinguishable from those seen in lichen planopilaris. This view has been disputed by some researchers because the lymphocytic infiltrate and fibrosis selectively affect the intermediate and the vellus hair follicles of the frontal margin and eyebrows. The reason for this selective involvement is still unknown.

The study reports four new familial cases of FFA including two families with involvement of three members. There has been a scarcity of reports of familial cases of FFA been published in the literature. The prevalence of men among familial cases of FFA in the current study is 12·5%, which is remarkably higher. Male cases have rarely been reported with few showing an extensive loss of body hair involving bilateral axilla, limbs, and pubic area.

Various conditions need to be considered in the differential diagnosis of FFA. A familial high frontal hairline may be present in some women which usually has an early age of onset and there is no associated scarring, no loss of eyebrows and no perifollicular erythema.

Elewski BE, Rich P, Pollak R, Pariser DM, Watanabe S, Senda H, et al. Efinaconazole 10% solution in the treatment of toenail onychomycosis: Two phase III multicenter, randomized, double-blind studies. J Am Acad Dermatol 2013;68:600-8.

Distal lateral subungual onychomycosis (DLSO) a progressive fungal nail infection leads to destruction and deformity of toenails and less frequently, fingernails. Topical lacquer treatments have negligible efficacy, oral treatments, although more efficacious are limited by drug interactions and potential toxicity. This study aimed at evaluating the safety and efficacy of efinaconazole 10% solution (efinaconazole), the first triazole antifungal developed for DLSO. In 2 identical, multicenter, randomized, parallel groups, DB, vehicle-controlled studies, patients with mild to moderate toenail DLSO (defined as 20-50% clinical involvement of the target toenail, without dermatophytomas or matrix [lunula] involvement) were randomized to receive efinaconazole 10% solution or vehicle.

Enrolled patients were randomized to receive efinaconazole or vehicle (3:1 ratio) self-applied once daily for 48 weeks without debridement, followed by a treatment-free 4-week follow-up. Assessment for efficacy and safety was carried out at baseline, 12-weekly intervals and final visit (week 52). The primary end point (complete cure) and secondary end points were assessed at week 52.

A total of 1655 patients were randomized (study 1: 870, study 2: 785) at 118 sites. Patients were randomized to efinaconazole 10% solution (study 1: 656, study 2: 583) or vehicles (study 1: 214, study 2:202). The mean toenail target area of involvement was 36.7% and 36.3% (studies 1 and 2, respectively) and the mean number of affected non target toenails was 2.8 in each study. 1436 (86.8%) patients and 1420 (85.8%) completed the 48-week and 52 weeks respectively. Mycologic cure rates were significantly greater with efinaconazole (study 1: 55.2%, study 2: 53.4%) compared to vehicle (P <0.001). The primary end point, complete cure, was also significantly greater for efinaconazole (study 1: 17.8% vs. 3.3%, study 2: 15.2% vs. 5.5%, P < 0.001). Treatment success (percent affected target toenail [0-#10%]) for efinaconazole ranged from 21.3% to 44.8% in study 1 and from 17.9% to 40.2% in study 2, compared with 5.6% to 16.8% and 7.0% to 15.4%, respectively, with vehicle.

Comment: Onychomycosis is one of the commonest dermatological conditions associated with significant physical and psychological morbidity. The toenails are affected in 80% of all the cases of onychomycosis; dermatophytes being the most commonly implicated etiologic agents. Prevalence has surged recently owing to comorbid conditions such as diabetes, avid sports participation, emergence of human immunodeficiency virus, and increased survival. Treatment becomes essential as spontaneous clearing does not occur, and it may predispose to cellulitis, and diabetic foot in diabetics. Furthermore untreated patients act as a reservoir for family contacts.

There is a huge disparity between the results of different drug trials targeting onychomycosis. The basic reason being the lack of consistency in defining and measuring cure. Secondly, efficacy assessments are often based on final evaluation at 48-52 weeks while it takes around 4-6 months and 12-18 months for a diseased finger or toenail to be replaced respectively.

Treatment with oral agents is limited by drug interactions and hepatitis. Drugs taken orally accumulate in the nail bed with suboptimal penetration in the lateral borders of nail. Desired blood levels of orally taken anti-fungals take some time to develop. However, they have the virtue of binding to the matrix tissue and are retained even after treatment cessation.

Topical treatment as opposed to oral therapies, offers a distinct advantage by allowing the patient to apply medication directly to the affected area; thus, decreasing the potential for serious adverse events such as drug toxicity and interactions, the topical preparations reach the nail within few hours of treatment and penetrate the nail plate, though the penetration is unpredictable especially in cases of dermatophytomas. Efinaconazole 10% (wt/wt) solution showed mycologic cure rates of 55.2% and 53.4% in study 1 and 2 respectively, which was significantly greater than the vehicle, with minimal side-effects and good tolerability.

Topical therapy provides desirable results in involvement limited to distal 50% of nail plate, three or four nail involvement, no matrix area involvement and superficial white onychomycosis. In view of this, efinaconazole can be considered as an agent for maintenance, although the risk-benefit profile is unknown.

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