Current Best Evidence

Current best evidence from dermatology literature - Part I

Seilding V, Hoffmann JH, Enk AH, Hadaschik EN. Analysis of high-dose intravenous immunoglobulin therapy in 16 patients with refractory autoimmune blistering skin disease: High efficacy and no serious adverse events. Acta Dermato-Venereol 2013;93:346-9.

High-dose intravenous immunoglobulin (IVIG) have been shown to be effective in treating severe autoimmune diseases that are refractory to standard immunosuppressive therapy. Although considered effective and safe in treating autoimmune blistering diseases, a clear evidence for its therapeutic effect besides case reports and case series is missing.

A retrospective analysis of 16 patients (10 patients with pemphigus vulgaris, 3 with pemphigus foliaceus, and one patient each with paraneoplastic pemphigus, bullous pemphigoid, and paraneoplastic bullous pemphigoid), refractory or relapsing disease under immunosuppressive combination therapy with at least two immunosuppressive drugs and who had received IVIG therapy for at least six full cycles, between January 2004 and July 2011 was done. The mean age and the mean duration from diagnosis to initiation of IVIG therapy was 50.4 years and 40.8 months, respectively. Patients had a mean of 2.9 immunosuppressive drugs prior to initiation of IVIG therapy. High-dose IVIG was administered at a total dose of 2 g/kg body weight intravenously per cycle over 2 days after ruling out the contraindications. Patients received IVIG every 4 weeks, and prior to discontinuation of IVIG the time between the cycles was extended to 5 or 6 weeks.

Efficacy of IVIG therapy was assessed with changes in skin symptoms, changes in autoantibody titers, and tapering of steroid dose. Laboratory blood tests including antibasement membrane antibodies and anti-intercellular epidermal antibodies were routinely performed. To measure efficacy of IVIG therapy, a score for each 6 months during the total period of 24 months was used:

- (Very good) – no skin symptoms; autoantibody titer: No change or lower titer,
- (Good) – skin symptoms ameliorated,; autoantibody titer: No change or lower titer,
- (Satisfactory) – skin symptoms unchanged; autoantibody titer: No change or higher titer,
- (Unsatisfactory) – skin symptoms deteriorated; autoantibody titer: No change or higher titer.

By the end of the 24-month observational period, most of the patients were still receiving IVIG. The mean total number of cycles per patient was 38.6. Adverse events were recorded in 87.5% of patients and in 56.3% of total infusion cycles. Headache (43.8%) and fatigue (43.8%) were the commonest side effects recorded. Only one patient reported petechiae after a single infusion cycle. Majority of patients had a very good score (43.8%, 75%, 61.5%, and 58.3%, respectively) in all of the four half-year periods. Also tapering of steroids up to a mean reduction of 75.8% in starting dose was possible without relapse in most patients.

Comment: IVIG is prepared from the pooled plasma of donors. Although initially used in the treatment of primary immunodeficiency syndromes, recently its use has been widely explored as an off-label indication in a variety of autoimmune and inflammatory conditions across multiple specialties.

Treatment of autoimmune bullous skin diseases can often be challenging. The treatment options primarily comprise systemic corticosteroids and a variety of immunosuppressants. Current treatment strategies are effective in most cases, but side effects of long-term immunosuppressive treatment are a limiting factor in some cases.

In addition, few patients fail to respond or experience frequent relapses. Some of the immunosuppressives have a long latency before benefit begins. The situation becomes all the more problematic in children for the fear of growth retardation. Secondary infection, which may be either systemic or localized to the skin, may

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occur because of the use of immunosuppressants and the presence of multiple erosions. Unlike most therapies for blistering disorders, IVIG is not immunosuppressive and has a favorable side effect profile.

This has allowed its use to expand dramatically over the past decade. It is generally accepted that the use of IVIG should be limited to patients who (1) fail conventional therapy; (2) have side effects or contraindications to conventional therapy that limits its use; and/or (3) have rapidly progressive disease or progressive disease despite conventional therapy.

This study demonstrates tapering of steroids up to a mean reduction of 75.8% from starting dose without relapse in most patients. Most of the reports utilizing IVIG at a dose of 2 gm/kg/cycle have shown a positive clinical outcome, decrease in pathogenic autoantibodies, and a steroid-sparing effect.

It has been well documented that IVIG causes a rapid decline in pathogenic autoantibody levels following which there is often a rebound increase, as in plasmapheresis. It has been hypothesized that use of IVIG along with rituximab or cyclophosphamide would be more beneficial in causing decline in pathogenic antibodies, suppressing the rebound increase and providing a sustained long-term remission with relatively low infectious complication rates.

In general, most published reports on IVIG have been retrospective analysis. There is a paucity of well-designed prospective trials. There is a need for randomized controlled trials for determining the efficacy and adverse effects of IVIG in the treatment of autoimmune bullous skin diseases.

Castanedo-Cazares JP, Lárraga-Piñones G, Ehnis-Pérez A, Fuentes-Ahumada C, Oros-Ovalle C, Smoller BR, *et al*. Topical niacinamide 4% and desonide 0.05% for treatment of axillary hyperpigmentation: A randomized, double-blind, placebo-controlled study. Clin Cosmet Investig Dermatol 2013;6:29-36.

Axillary hyperpigmentation is a frequent cause of cosmetic consultation among dark-skinned women from tropical areas, including Latin America. Currently, there is no widely accepted treatment for the disorder. It is usually treated with bleaching agents because it is considered a variant of inflammatory hyperpigmentation. This was a 9-week, randomized, double-blind, left–right axilla, placebo-controlled trial study conducted to assess the efficacy of niacinamide 4% and desonide 0.05% emulsions in the treatment of axillary hyperpigmentation.

Twenty-four women aged 19-27 years with hyperpigmented axillae (phototypes III-V) were randomly assigned to receive the study treatments in the axillary region. Improvement was assessed at baseline, then clinically and by colorimetry 9 weeks later. Quantitative evaluation including melanin, inflammatory infiltrates, NKI/BETEB, CD1a, CD68, and collagen type IV content was performed by histochemistry and immunohistochemistry, assisted by computerized morphometric analysis.

Both niacinamide and desonide induced significant colorimetric improvement compared with placebo; however, desonide showed a better depigmenting effect than niacinamide. A good to excellent response was achieved in 24% of cases for niacinamide, 30% for desonide, and 6% for placebo. Side effects, including local erythema, burning, pruritus, infection, and skin atrophy, were absent during the trial. In addition to the associated inflammatory cell infiltrates, a physical discontinuity of the epidermal basal membrane was found which improved after exposure to both drugs and was more evident in the desonide group.

Comment: Postinflammatory hyperpigmentation (PIH) is an acquired hypermelanosis occurring after cutaneous inflammation or injury. It can arise in all skin types, but is more frequent in individuals with darker skin (Fitzpatrick skin types IV to VI) as the melanocytes of darker-skinned individuals show an exaggerated response to cutaneous injury. PIH can have a significant psychosocial impact, which is well supported by various epidemiological studies that depict dyschromias. Axillary hyperpigmentation has not been extensively studied due to its primarily cosmetic nature and lack of any major and significant health implications. It has been proposed that axillary skin darkening is best defined as mild PIH, characterized by increased epidermal melanin production, following mild irritation or stimulation of the skin. The treatment of hyperpigmentation in these patients has remained challenging for dermatologists.

Axillary skin is distinctly different from those of other body sites, as it has reduced barrier integrity. Studies have shown cholesterol, ceramide 3, and lactic acid levels to be increased, and natural moisturizing factor amounts to be lower, cornified envelopes to be smaller

indicative of a shorter stratum corneum turnover, compared with the volar forearm.

Although the precise pathogenesis is unknown, it is thought to result from cytokines, inflammatory mediators, and reactive oxygen species. In some individuals, the axillary skin may face additional challenges including leaching of lipids and proteins from the stratum corneum by cleansing surfactants, or additional irritation induced by shaving and plucking which further impairs the natural barrier to exogenous irritants. Histological evaluation of female Filipino axillary skin has revealed that the trauma of underarm hair plucking is associated with melanosome leakage into the dermis and hence increased pigmentation, as well as mononuclear cell and macrophage infiltration.

This study reveals that niacinamide and desonide have depigmenting properties in women with axillary hyperpigmentation along with the added advantage of improvement in the physical discontinuity of the epidermal basal membrane. However, multicentered trials including a large number of patients would be helpful in providing a better interpretation.

Klein A, Steinert S, Baeumler W, Landthaler M, Babilas P. Photoepilation with a diode laser vs. intense pulsed light: A randomized, intrapatient left-to-right trial. Br J Dermatol 2013;168:1287-93.

Photoepilation with lasers or intense pulsed light (IPL, 590-1200 nm) sources is a widely used efficient and safe treatment modality for the removal of unwanted hair. Devices currently in use work on the basis of the selective photothermal destruction of hair follicles, which is based on the principle of selective photothermolysis. This randomized controlled trial (RCT) was undertaken to compare the efficacy, side effects, and patient-rated efficacy of two popular light devices for hair removal, a diode laser (DL) and an IPL source.

IPL and DL treatments were evaluated in 30 participants with a mean age of 33·7 years (skin types II–III) with unwanted axillary hair. Six treatments with each device were carried out at 4-week intervals. The two axillary regions of each patient were randomized to the two competing procedures. After each laser treatment, study subjects were evaluated for immediate side effects, such as burning, edema, and blistering. A visual analog scale (VAS) ranging from 0 to 10 was used for the self-assessment of pain (0 = no pain, 10 = maximum pain) at every treatment visit. The mean score for all six visits was obtained. For the quantitative evaluation of hair growth, the three regions of interest of each axillary region were photodocumented at each visit with a handheld dermatoscope. Final assessment was conducted 12 months after the last treatment by means of hair counts using close-up photographs. The primary endpoint was reduction in hair growth, analysed on an intention-to-treat and last-observation-carried-forward basis (n = 30), and secondary endpoints were patient-rated efficacy, treatment-related pain, adverse effects, and treatment duration.

All participants completed the 3- and 6-month follow-up evaluations (visits 7 and 8), but only 25 volunteers were available for the 12-month follow-up (visit 9). Both devices significantly reduced hair counts. Mean reductions from baseline (3 and 12 months after the last treatment) were 59.7% and 69.2% for DL and 42.4% and 52.7% for IPL treatment (P < 0·01), respectively. DL treatment induced significantly more pain [3.7 ± 2.1 (DL) vs 1.6 ± 1.4 (IPL); P < 0.01; VAS] but could be conducted faster [33.1 ± 3.8 s (DL) vs 40.1 ± 5.0 s (IPL); P < 0.01]. No severe side effects were observed for either therapy.

Comment: Advances in laser technology have led to the establishment of laser hair reduction as a safe modality for the treatment of unwanted hair on any body part. An ideal patient has thick dark terminal hair, white skin, and a normal hormonal status. There is a paucity of data regarding the safety and efficacy of lasers in dark-skinned individuals.

Studies in the past have compared diode and Nd: YAG laser in terms of efficacy for hair reduction with most of them showing DL to be more comfortable and efficacious. However, without the use of topical anesthetics, patient preference might be based on pain level during the treatment session.

Few studies done in the past have directly compared long-term outcomes of lasers with IPL with both the lasers and light devices showing similar long-term efficacy contradicting the results of this study. Current long-term evidence on efficacy of IPL is sparse. Few trials comparing diode with IPL have shown similar efficacy at 6 months after treatment contrary to the results in this study.

In this study, all sessions were repeated at 4-week intervals. The resting phase for axillary hair tends to be longer when compared with the scalp and beard

hair. Doing the sessions too frequently might lead to a temporary suppression rather than destruction of hair follicle. Controlled trials would be required to differentiate the hair reduction in the long term achieved when sessions are done at 4 weekly intervals versus increasing the gaps after second session.

Careta MF, Fortes AC, Messina MC, Maruta CW. Combined treatment of earlobe keloids with shaving, cryosurgery, and intralesional steroid injection: A 1-year follow-up. Dermatol Surg 2013;39:734-8.

Earlobe keloids are benign, fibrous proliferations occurring in predisposed persons at sites of cutaneous injury (ear piercing, burns, or surgical procedures). Twelve consecutive patients with earlobe keloids were treated with a combination of surgery and cryosurgery. The surgical procedure consisted of shaving after local anesthesia leaving 1-2 mm of the remaining lesion at the borders. Cryosurgery (liquid nitrogen spray) of the underlying tissue followed it. One cycle of freezing was performed (freezing time 60 s). Patients were evaluated 7 and 30 days after the surgical procedure. At day 30, cases with persistent keloid lesion received adjuvant therapy with intralesional injection of triamcinolone acetonide (10-20 mg/mL). Monthly evaluation was done. The mean posttreatment follow-up was 12 months. Major response, moderate response, and failure was defined as 80%-100% reduction in keloid thickness, 50%-80% reduction in keloid thickness, and improvement of less than 50% or complete relapse after treatment, respectively.

After 1 year, major and moderate response were observed in 9 cases (75%) and 2 cases (16%), respectively; 1 case had relapse 5 months after surgery. The number of intralesional triamcinolone injections varied from none to 4.

Comments: Earlobe keloids are benign fibrous proliferations characterized by an excess of collagen deposition. They occur in predisposed individuals at sites of trauma, ear piercing, burns, or surgical procedures. The incidence is higher in blacks and Asians when compared with Caucasians.

They are commonly encountered in day-to-day clinical practice and pose a challenging management problem and distinctive cosmetic implications. Clinically, they appear as shiny, smooth, globular growths on one or both sides of the earlobe. Pruritus, pain, and paresthesias can be another source of distress for some of these patients.

Various therapeutic modalities are available for treatment of keloids. There is no consensus regarding the optimal or best management of keloids. Surgical excision alone has been found to have a low success rate with a high incidence of recurrence in previous studies. Intralesional injection of corticosteroids is one of the mainstays in the management of earlobe keloids. Monotherapy with intralesional injection of steroids has been found to alleviate the subjective symptoms in most of the studies with variable success in improving the objective symptoms.

In the recent literature, surgical excision along with adjuvant therapy is recommended. There is no standardized protocol regarding the administration of intralesional corticosteroids. Some have advocated the instillation of steroids after removal of the sutures followed by weekly or fortnightly injections. Few have also advocated the use of intralesional steroids prior to surgical excision.

Cryosurgery as monotherapy for the treatment of earlobe keloids has shown diverse results. The recently introduced intralesional cryoneedle method has been found to be simpler and safer to use, requiring less postoperative care.

In this study, major response was observed in majority of the cases at 1 year of follow-up with shaving, cryotherapy, and intralesional steroids. The success rate of combination of surgery and triamcinolone acetonide injection has shown great variation across different studies with some exhibiting unsatisfactory response. Here the treatment modality consists of three different treatment techniques. The favorable response illustrated probably reflects the synergism of the combinations. However, in a given patient, the location, size, depth, and duration of earlobe keloids are critical factors in deciding the individualized modality of treatment.

Although this study reveals good comprehensive results, studies dealing with duration of keloids comparing with various treatment responses need to be carried out.

Poot AM, Diercks GF, Kramer D, Schepens I, Klunder G, Hashimoto T, *et al*. Laboratory diagnosis of paraneoplastic pemphigus. Br J Dermatol 2013. [In press]

Paraneoplastic pemphigus (PNP) is a multiorgan disease characterized by antibodies against plakins, desmogleins,

and the alpha-2-macroglobulin-like-1 (A2ML1) protein, in association with an underlying neoplasm. This study was undertaken to compare the diagnostic value of different laboratory techniques in the serological diagnosis of PNP by performing immunoblotting, ELISA for envoplakin (EP_ELISA), anti-Dsg1, anti-Dsg3, BP180, BP230, indirect immunofluorescence (IIF) on rat bladder, radioactive immunoprecipitation (IP), and a nonradioactive combined IP-immunoblot assay on the sera of 19 PNP (median age of 56.6 years) and 40 control patients. The diagnosis of PNP was made if patients fulfilled the revised criteria proposed by Anhalt in 2004 and Zimmerman in 2010.

Sensitivities for anti-EP ELISA, rat bladder IIF, immunoblotting (IB), radioactive IP, and nonradioactive IP were 63%, 74%, 89%, 95%, and 100%, respectively, with specificities ranging from 86% to 100%. Low sensitivity and specificity were observed with BP180- and BP230-ELISAs.

Comment: PNP is a distinct autoimmune blistering dermatosis occurring in association with various neoplasms. The clinical features consist of recalcitrant, painful oral erosions that may be accompanied by polymorphic cutaneous eruptions and systemic involvement. It is characterized by the presence of autoantibodies against desmoglein 3 (Dsg3) (130 kd), desmoglein 1 (Dsg1) (160 kd), envoplakin (210 kd), periplakin (190 kd), desmoplakin I (250 kd), desmoplakin II (210 kd), bullous pemphigoid antigen 1 (BPAG1) (230 kd), plectin (>400 kd), and a previously unidentified 170-kd protein which has recently been identified as A2ML1, a broad-range protease inhibitor expressed in stratified epithelia.

Histological findings vary considerably according to the clinical presentation and age of the lesions with predominant suprabasal acantholysis in noninflammatory blisters, whereas interface and lichenoid dermatitis in erythematous inflammatory maculopapular lesions. DIF is negative in half of PNP patients and false negatives are also common, attributable to lichenoid lesions and necrotic tissue in the mucosal biopsies. The presence of autoantibodies to plakins is a characteristic feature with highest specificity for envoplakin and periplakin followed by desmoplakins. Plakin autoantibodies, however, have been found in other conditions such as pemphigus vulgaris, pemphigus foliaceous, erythema multiforme, and toxic epidermal necrolysis, hence demonstration of antiplakin antibodies alone is not sufficient to point toward the diagnosis of PNP.

IP has been found to be the most sensitive and specific test for demonstrating antiplakin antibodies in most of the studies, qualifying as a major diagnostic criteria for PNP. However, tedious nature, cost, and lack of easy availability are the limiting factors. This study shows sensitivity of radioactive IP assay to be superior to IB, IIF on rat bladder, and EP-ELISA. Also, the nonradioactive IP showed marginally higher sensitivity than the radioactive IP. In the absence of IP, combination of IB and rat bladder-IIF may be used as the first serological test for confirming the diagnosis of PNP.

However, more studies with larger number of patients are required to support the findings, which would be of a substantial help in accurately diagnosing this often-fatal disease with a myriad of variable cutaneous morphologies and the morbidity of recalcitrant mucosal lesions.

Moftah N, Moftah N, Abd-Elaziz G, Ahmed N, Hamed Y, Ghannam B, *et al*. Mesotherapy using dutasteride-containing preparation in treatment of female pattern hair loss: Photographic, morphometric and ultra structural evaluation. J Eur Acad Dermatol Venereol 2013;27:686-93.

Female pattern hair loss (FPHL) is one of the most common causes of hair loss, affecting 50% of women in the age of 50 years. Treatment of FPHL is frustrating for both patients and doctors. This study including 126 female patients with FPHL was carried out to evaluate the efficacy and safety of mesotherapy using dutasteride-containing preparation. The patients were classified into two groups: Group I (86 patients) (mean age 34.1 ± 6.6 years) and group II (40 control patients) (mean age 34.8 ± 7.2 years) injected with dutasteride-containing preparation and saline, respectively. Patients received 12 sessions over a period of 16 weeks and were evaluated at the 18th week by photographic assessment, hair pull test, hair diameter, and patient self-assessment. Ultra structural evaluation was done for three patients using five of the randomly epilated hairs from the vertex as described by Wyatt and Riggott, before and at the 18th week using scanning electron microscope. Photographic improvement was seen in 62.8% of patients compared with 17.5% in control group. Significant improvement in mean hair diameter and

decline in mean number of epilated hairs were seen in group I. Side effects were minimal with no statistically significant difference between the two groups. Ultra structural examination of pretreated hairs revealed absent cuticle in one patient and focal destruction of the cuticle in the second patient, which reappeared in both after therapy. There was a negative correlation between degree of improvement and duration of FPHL ($P < 0.05$).

Comment: FPHL is the most common cause of alopecia in women characterized histologically by increased numbers of miniaturized hair follicles. Although medically benign, the impact is predominantly psychological leading to distress, low self-esteem, depression, and impaired quality of life in a significant number of affected females.

The goal of treatment is to arrest the progression of alopecia and stimulate new hair growth. Two main pharmacological options currently widely used are antiandrogens and minoxidil, which need to be continued indefinitely to attain and maintain response.

Mesotherapy has gained a lot of attention in recent past; however, the scientific basis is not established. The US FDA in view of lack of documented evidence has not yet approved it. On theoretical grounds, it can be hypothesized that dutasteride might be more efficacious than finasteride as the latter being a selective inhibitor of type 2 isoenzyme of 5-alpha reductase has the capability to reduce serum dihydrotestosterone levels by about 70%, whereas dutasteride inhibits both isoenzymes inducing more than 90% reduction in the dihydrotestosterone levels. Longer half-life of dutasteride when compared with finasteride has been a limiting factor for the former's use.

In this study, dutasteride administered by meso therapy demonstrated significant increases in target area hair count in comparison to placebo, as early as 12 and 24 weeks. In few studies assessing the efficacy and safety of five alpha inhibitors in androgenetic alopecia, dutasteride was found to be superior to finasteride at 12 and 24 weeks in male pattern hair loss. Also, few reports showed noteworthy response with dutasteride in patients with limited improvement after 6 months of finasteride. This study results reiterate the above findings.

Current treatment options are limited, and even in positive responders a considerable time delay occurs before improvement is apparent. In cases of advanced alopecia (Ludwig grade III) and failure with aforementioned medical therapies, surgical management remains an important option. Dutasteride may be considered as an additional treatment option, following further studies in cases of grade I and II FPHL.

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