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Novel Dermatologic Uses of the Immune Response Modifier Imiquimod 5% Cream

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ABSTRACT

Imiquimod is the first of a new class of drugs to emerge in the treatment of various dermatologic disorders. As an immune response modifier, it has been shown to have potent antiviral and antitumor properties through the stimulation of innate and cell mediated immune pathways. It is currently approved for the treatment of external genital and perianal warts, but has also been found to be an effective treatment for a host of other virus-associated dermatologic lesions, including common and flat warts, molluscum contagiosum and herpes simplex 2. Oncological lesions showing improvement with the use of imiquimod include basal cell carcinoma, actinic keratosis, squamous cell carcinoma in situ, malignant melanoma, cutaneous T-cell lymphoma, and cutaneous extramammary Paget's disease. Recent case studies have also found this product to be effective for treating keloids, infantile hemangioma, porokeratosis of Mibelli, leishmaniasis, and tattoo removal. This extensive array of disorders treated successfully with imiquimod warrants further study of this novel and valuable drug.

Key Words: imiquimod, immune response modifier

As an immune response modifier, imiquimod 5% cream (Aldara™, 3M) indirectly acts to enhance the body's natural ability to heal through the induction of innate and cell mediated pathways. Stimulation of these immune pathways leads to the synthesis and release of cytokines, most often interferon- α , tumor necrosis factor- α , interferon- γ and interleukin-12. Activity of natural killer cells, macrophages, B lymphocytes, and Langerhans cells is also enhanced significantly.¹ At present, imiquimod is approved as a topical, patient-applied treatment option for external genital and perianal warts produced by human papillomavirus (HPV).² The efficacy of treatment with imiquimod has been shown to effectively clear external genital warts from 50% up to 75.5%, with the higher numbers present in uncircumcised males, as well as in female patients.^{3,4} Owing to its broad immunologic properties, imiquimod has also been documented as a safe and effective treatment for several other skin conditions. In 2001, Sauder categorized a range of conditions that was reported to have been successfully treated with imiquimod into virus-associated conditions, oncological conditions, and other conditions.⁵ Since then, the array of skin conditions successfully treated with imiquimod has expanded.

Virus-associated conditions

Human papillomavirus (HPV)

The antiviral activity of imiquimod has been useful for clearing genital warts produced by HPV, but indirectly. It is not specifically targeted against the HPV types

(HPV 6 and 11) that result in genital warts. Therefore, patients with nongenital warts caused by other subtypes of HPV are felt to be prime candidates for treatment, and several case reports illustrate imiquimod's efficacy in these patients. Fifty patients with common warts were treated with imiquimod once daily for 5 consecutive days over a span of 12 weeks; 30% showed complete clearance and 26% showed a reduction in wart size greater than 50%.⁶ Muzio, et al, reported 10 cases of recurrent common warts, with 8/10 patients showing total remission after application of imiquimod under occlusion once daily for 4 weeks, with no recurrences reported at 3-month follow-up.⁷ In a case report, imiquimod applied nightly 3 times/week demonstrated its potential use in recalcitrant facial flat warts, with complete clearing after 3 weeks of therapy.⁸ Successful treatment of HIV-positive patients with common warts was reported with the length of treatment ranging from 4-12 weeks.^{6,9} Other successful cases of treating warts in immunosuppressed patients were reported using a combination of imiquimod with CO₂ laser therapy and occlusive treatment.¹⁰ In addition to HPV-induced common warts, Stockfleth, et al, reported a case of HPV DNA-positive generalized stucco keratosis, successfully treated with imiquimod, 3 times/week for 5 weeks.¹¹

Molluscum contagiosum virus (MCV)

Imiquimod has been shown to be effective in other non-HPV associated virally-induced conditions as well. Molluscum contagiosum (MC), caused by a large double-stranded DNA virus of the *Poxviridae* family, has been successfully treated with imiquimod in both children and adults. Barba, et al, treated the MC lesions of 13 children with imiquimod in an open-label safety study for 4 weeks, with full resolution of baseline target lesions in 12/13 children and no evidence of systemic toxicity. The one patient who did not complete the study experienced severe erythema, local superficial forehead erosion, and hypopigmentation that slowly resolved.¹² Liota, et al, also included children in their patient population, as the molluscum contagiosum virus (MCV) is most commonly seen in young children, sexually active adults, and in some immunosuppressed patient populations. In a 16-week trial using imiquimod 3 times/week, 14/19 immunocompetent adults, 4/4 HIV-positive adults, and 6/13 children had resolution of their MC lesions, with more local inflammatory and pruritic reactions occurring among the children. In areas expected to have greater penetration of a topical agent (e.g., the axillae) clearing was more consistently observed.¹³ An open-label study also examined imiquimod's effect on patients with common warts or MC, and showed total clearance of MC lesions in 8/15 (53%) patients or a >50% reduction in molluscum size

in 4/15 (27%) patients. The mean duration of treatment was 9.8 months (range 2-24), and there were no differences found with regard to gender or HIV status.⁶ As MCV does not develop latency, but evades the immune system in other ways, the clearance of MC lesions tends to reflect long-term cure.¹³ Several case studies have also illustrated the efficacy of imiquimod for treating MC lesions of immunocompromised populations. Buckley, et al, described the case of an HIV-1 positive woman with extensive disfiguring MC lesions who had failed cryotherapy, 0.5% podofilox, and 0.5% tretinoin.¹⁴ Brown, et al, described a similar case of MC, which had also failed conventional therapies with cryotherapy and trichloroacetic acid crystalline solution.¹⁵ In both cases, topical imiquimod resulted in full clearance of the treated lesions with no systemic adverse effects, but stable postinflammatory hyperpigmentation developed.

Herpes simplex virus 2 (HSV-2)

Topical imiquimod offers an alternative for treating herpes simplex virus (HSV) infections, particularly in the setting of emerging resistance. A 34-year old HIV-positive man who developed a HSV-2 infection of the penis resistant to acyclovir, valacyclovir hydrochloride, and famciclovir was successfully treated with imiquimod applied 3 times/week for 1 week, with no recurrences after 1-month of follow-up. This report may support the use of topical imiquimod as an effective treatment for HSV infections, particularly in the setting of acyclovir resistance or unresponsiveness.¹⁶

Oncological and oncologically related conditions

Basal cell carcinoma (BCC)

A series of clinical trials and case reports document the effectiveness of imiquimod for treating superficial or nodular basal cell carcinomas (BCCs) on low-risk sites.¹⁷⁻²² Efficacy seems to be dose-related. For superficial basal cell carcinoma, cure rates vary from 69.7% up to 100%.^{19,20} Nodular BCC cure rates are just below 80%, and do not reach the level of complete clearance expected of a first line monotherapy.²²⁻²⁴ Currently, there is no consensus as to the most effective treatment regimen using imiquimod, and complete response has been reported in as little as 6 weeks up to 18 weeks.^{20,26} Optimal dosing to minimize cutaneous side-effects and maximize efficacy has not been determined; studies suggest that treatment should be dosed 3-5 times/week. Rest periods have also been recommended.²⁰ Complete (100%) compliance with dosing did not appear necessary to achieve a complete efficacy response.²⁰ Though statistically significant correlation has been established between the most intense erosion reaction assessed by the investigator and a complete response, twice-

daily application was reported to produce unacceptable skin reactions. Daily application seems the most suitable for use in clinical practice on the basis of efficacy, tolerability, potential cost of treatment, and likelihood of compliance for a lengthy period of treatment.^{20, 24} The cosmetic outcome has been excellent.^{20, 22} Special cases of BCCs treated with imiquimod include a large (5x6 cm) superficial BCC,²⁵ a patient with Basal Cell Nevus Syndrome and multiple BCCs,^{26, 27} and a report of two siblings with xeroderma pigmentosum, in whom topical imiquimod reduced the rate of new tumor formation, permitting dermatologists to “keep up” with the surgical treatment of new lesions.²⁸ Further clinical trials are required to confirm efficacy in larger BCCs and BCCs with aggressive growth patterns.

Actinic keratosis (AK)

Imiquimod was documented in a few studies as a useful treatment option for AK. A double-blind pilot study²⁹ examined 41 AK patients applying imiquimod or a vehicle cream in different dosing groups to three target AKs for up to 16 weeks, with clinical resolution of all target lesions. In another randomized, double-blind study,³⁰ 36 patients with AK lesions applied imiquimod or a vehicle cream 3 times/week for 12 weeks or until resolution, which occurred in >80% of patients. Six case reports of men with AK were described, where imiquimod was applied 3 times/week for 6-8 weeks. In the event of a local skin reaction, treatment was modified to 2 times/week. All of the AK lesions successfully cleared and there were no reports of recurrence (ranging from 2-12 months post-treatment).³¹ In a small trial involving 22 patients, their AKs were treated with imiquimod initially at 3 times/week for 8 weeks or until there was total clearance of the lesions.³² By the end of the study, a significant reduction in the average number of lesions per patient was observed. Salache, et al, used imiquimod to treat 25 AK patients in specific dosing cycles, alternating treatment weeks with weeks of rest and continuing such treatment until complete clearance was achieved.³³ This study, along with others requiring rest periods for local adverse reactions, underscores the need to determine appropriate dosing regimens for patients with AK and other cutaneous lesions.

Squamous cell carcinoma *in situ* (Bowen’s disease)

Treatment modalities for squamous cell carcinoma *in situ* (Bowen’s disease) often have significant risk of scarring, deformity, and poor cosmetic appearance. Surgery on common areas for Bowen’s disease (lower limbs, head, neck) may be anatomically difficult. With this in mind, Mackenzie-Wood, et al, treated 16 patients in a phase II, open-label study, where imiquimod was applied to biopsy-proven plaques of Bowen’s disease once daily for 16 weeks.

Six-week post-treatment biopsies revealed no residual tumor in 14/15 patients (the 16th patient was unavailable for biopsy), although 6 patients found it necessary to stop treatment early due to intense local skin reactions during the study.³⁴ Several case reports have illustrated the efficacy of imiquimod in treating Bowen’s disease of the penis.^{35, 36} A 65-year old circumcised male applied imiquimod nightly until intense local erythema and erosions developed. A rest period was given before treatment was resumed. Follow-up at 18-months post-treatment revealed no residual or recurring tumor and no evidence of scarring, deformity, or loss of function.³⁶ Imiquimod has also been shown to be effective in combination with 5% fluorouracil (5-FU) therapy in immunosuppressed populations. A recent case study reported an HIV-positive male with perianal Bowen’s disease treated with 5-FU and imiquimod in the same time frame. By 16 weeks, clinical and symptomatic improvement occurred without persisting or recurring lesions.³⁷ Smith, et al, also presented five cases of renal transplant patients treated with imiquimod and 5-FU for Bowen’s disease in multiple areas following their transplants. Topical application of both imiquimod and 5-FU was instigated 3 times/week until complete resolution of the lesions was achieved in all of the patients, with no residual lesion at 3-15 month post-treatment follow-up visits.³⁸

Bowenoid papulosis

Bowenoid papulosis is histologically seen as a carcinoma *in situ*, despite the benign course of the condition. In 2001, a case report described the effect of imiquimod applied on alternating days for 10 days, or until the skin became visibly irritated and a new dosing schedule was assigned (application once daily for another 10 days, washed off after 2 hours). Complete clinical resolution was noted within 8 weeks and histology revealed no persisting or recurring disease. The patient remained clinically clear after more than 18 months off treatment.³⁹

Vulvar intraepithelial neoplasia (VIN)

A large percentage of vulvar intraepithelial neoplasias (VIN3) have been shown to harbor human papillomavirus (HPV). Imiquimod, an effective treatment for external and perianal genital warts caused by HPV, is thought to be a potentially beneficial treatment for patients with VIN3 of viral (HPV) etiology. A prospective study of 15 patients with high-grade VIN3 examined the effects of imiquimod, self-applied 3 times/week to vulvar lesions for 16 weeks. Only 13/15 patients were able to complete the study, and of those, only 4 showed visible clinical improvement in the state of their condition. The rest of the patients did not improve using imiquimod, although local side-effects such as soreness and burning limited the frequency of cream

application, and therefore may have contributed to the patients' lack of improvement.⁴⁰ Four cases of imiquimod-treated VIN3 were also reported, with a regimen of self-applied imiquimod to vulvar lesions 3 times/week until all lesions cleared, for up to 16 weeks. Three of the patients had recurrence of their lesions, with one of the recurrences occurring (and treated with further imiquimod use) during the trial. Other recurrences developed 1 year post-treatment, inside and outside the original field of treatment. These patients were only instructed to use imiquimod during the time of the study, and it is postulated that extended treatment and long-term follow-up may prevent future recurrences.⁴¹

Melanoma

Imiquimod has also been useful for treating melanoma. In a case report, a patient reluctant to have a large lentigo maligna of the scalp excised underwent a complete clinical and histological cure after application of imiquimod for 7 months to an initial test area inside the lesion, then to the entire lesion. No clinical recurrence was reported at 9-month follow-up. The recommended treatment for lentigo maligna is conventional surgery, using a 5-10mm margin. Imiquimod may be a novel treatment option worthy of consideration for carefully selected patients in whom more traditional therapy is not considered feasible.⁴² Likewise, a 50-year-old female suffering from disseminated cutaneous metastatic melanoma lesions was treated with imiquimod 3 times/day with continuance of dacarbazine. Lesions were too initially widespread to be treated with excision or radiotherapy, and failed to improve after a cycle of dacarbazine alone. After 12 weeks of treatment with imiquimod, metastases were no longer detected.⁴³

Cutaneous T-cell lymphoma (CTCL)

A case of cutaneous T-cell lymphoma (CTCL) recently reported complete clearance of clinical and subclinical disease after 4 months of therapy with imiquimod. There was no recurrence at the treatment site at 10-month follow-up. The authors have initiated a double blind, placebo-controlled trial to better evaluate the efficacy of imiquimod in the treatment of CTCL.⁴⁴

Cutaneous extramammary Paget's disease (EMPD)

Extramammary Paget's disease is an infrequent epidermal malignancy, occurring most commonly in the anogenital and vulvar regions. Berman, et al, treated a case of cutaneous scrotal EMPD with once-daily, self-applied imiquimod over a period of 6 weeks. Though local erythema developed in the treatment area, no systemic symptoms were noted and clinical resolution occurred by week-4 of treatment, with no remaining pathology at 6-month follow-up.⁴⁵ Two other cases of perineal and genital EMPD have

also been recently reported, with clinical cure occurring after applying imiquimod on alternating days of the week for 7.5 to 12 weeks. Although it was concluded that this treatment modality was a much less invasive therapeutic option, both cases were associated with systemic symptoms that included flu-like symptoms (malaise, fatigue, low-grade fever), as well as nausea and vomiting.⁴⁶

Actinic cheilitis

A retrospective review of 15 patients receiving topical imiquimod as a single agent 3 times/week for the treatment of actinic cheilitis was recently published. Clearance of the treated area was reported in six patients after 4 weeks of treatment, and in the remaining nine patients after week 6. Since it is possible for this condition to progress to invasive squamous cell carcinoma, it is mentioned in this category of oncologically-related conditions.⁴⁷

Other conditions

Keloids

Berman and Kaufman recently examined the effects of post-operative, topical application of imiquimod to 13 keloids excised from 12 patients. It was applied nightly for 8 weeks, with no recurrence of keloidal growth among the 11 keloids (10 patients completed the study) evaluated at 24 weeks, a rate that was lower than previously reported recurrence rates. The two remaining patients, though lost to follow-up, had completed the 8-week treatment phase and had no keloid recurrence at the time they left the study. Mild local reactions occurred, but were resolved with temporary discontinuation, and no systemic effects were noted.⁴⁸

Infantile hemangioma

Imiquimod, used to treat two cases of infantile hemangioma of postnatal onset showed complete resolution of these scalp lesions in the proliferative state within 3-5 months. Though the development of erythema and crusting necessitated resting periods, both cases showed virtually complete clinical regression without scarring and neurologic abnormalities. The authors have launched a larger clinical study with pathologic correlation and a mechanism-oriented investigation.⁴⁹

Porokeratosis of Mibelli

Agarwal and Berth-Jones recently reported a patient with a clinical and histological diagnosis of porokeratosis of Mibelli, successfully treated with imiquimod once-daily for 5 days/week. The initial 3-month treatment showed no response. Subsequently, the same dosage and frequency of imiquimod was used, but under occlusion with an adhesive polythene dressing (Tegaderm[®], 3M). The lesion cleared after 5 weeks of treatment, without recurrence at 1-year follow-up. The authors suggested that in the case of porokeratosis of Mibelli,

imiquimod application may need to be followed by occlusion due to its inability to penetrate the lesion sufficiently. Although it is possible that occlusion alone would have proven to be therapeutic, the authors believe it is unlikely.⁵⁰

Leishmaniasis

An open-label, prospective study of combined meglumine antimonate plus imiquimod therapy was conducted in 12 patients with cutaneous leishmaniasis who had previously not responded to a complete course of meglumine antimonate monotherapy. All of the patients responded well to this combination therapy, and 90% were cured at the 6-month follow-up period. Although imiquimod as a solo agent has previously failed to be effective in the treatment of cutaneous leishmaniasis, this study shows that there may be a synergistic effect between imiquimod and meglumine antimonate responsible for the cure of these cases of cutaneous leishmaniasis.⁵¹

Tattoo removal

Imiquimod was used for experimental nonsurgical tattoo removal in a guinea pig model using topical imiquimod. Application began 6 hours after tattooing, and treatments were applied every 6 hours for up to 7 days, with no visible tattoo showing at day 28. This is consistent with greatly diminished or no dye evident on histopathology, but is associated with fibrosis and the loss of dermal appendages. This study addressed the treatment of acute-phase tattoos. The authors suggested that early clinical intervention with imiquimod may eventually play a role in the nonsurgical management of tattoo allergy, especially if laser therapy is not an option.⁵²

Conclusion

Imiquimod 5% cream is currently approved for use in genital and perianal warts. However, it may also be an effective treatment for a variety of other entities. As a topical agent, application of imiquimod is convenient because it is patient-applied and reduces the necessity for surgical excision. It is important to note that recent literature regarding imiquimod's newer uses consists mostly of case studies. Additional assessment in controlled studies is warranted for each of these conditions. Such studies should take place over longer periods of time, during and after the treatment phase and attention should be paid to the dosing frequency. Furthermore, because imiquimod induces production of interferons, and enhances Th1 cell-mediated immune responses, it can be potentially useful in the treatment of conditions that respond to interferon therapy, such as Kaposi's sarcoma and chronic granulomatous disease.⁵³ Other potential uses may stem from imiquimod's ability to also inhibit Th2 responses, and therefore may be useful in treating such entities as atopic dermatitis.⁵

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Dear Reader,

Starting with the current issue, Skin Therapy Letter will include a regular section devoted to dermatologic surgery. Entitled "Advances in Dermatologic Surgery," this section will highlight evolving clinical topics in laser, cosmetic, oncologic, and reconstructive skin surgery. Prominent practitioners will be asked to share their expertise in simple, concise language. The goal will be to impart practical tips about procedure indications, benefits and limitations, patient selection, and treatment technique. We hope that despite the brevity of the articles, the emphasis on new developments will provide value to novice readers as well as more experienced cosmetic dermatologists and dermatologic surgeons.

We invite you to consider submitting articles to this column. Should you have an area of special interest, please contact either of us to discuss the possibilities. Additionally, we encourage you to communicate your comments and criticisms regarding the pieces that we publish.

In the inaugural article that follows, Dr. Lisa Donofrio explains the subtleties of autologous fat transplantation, or "facial rebalancing." She begins with an enlightening review of the aesthetic and practical foundations of the procedure, and continues with a detailed itemization of cautions, technique points, and other helpful advice garnered from extensive experience.

Jeffrey S. Dover, MD and Murad Alam, MD

Fat Rebalancing: The New "Facelift"

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ABSTRACT

The fat compartments of the face undergo changes and are responsible for age-related alterations in facial shape. The overlying skin responds to changes in fat in much the same way as a garment clings or sags to the body underneath. By rearranging the underlying fat via suction and fat replacement techniques, a younger-shaped face can be achieved without conventional excisional surgery.

Key Words: fat rebalancing, aging

Aesthetics of the Aging Face: Gravity vs. Fat

Age-related morphologic changes in the face are due largely to fat redistribution. From infancy through adulthood, it is fat that characterizes the face's shape. A baby has an identifiable distribution of fat in its chubby cheeks, jowls and neck rolls. Interestingly, this distribution occurs again in the older adult, but we ascribe it to loose skin and blame gravity.

Gravitational aging is the target for much of conventional cosmetic surgery. The premise of gravitational descent has founded surgical corrections like face, brow, and neck lifts, blepharoplasty, and laser resurfacing. But to consider gravity the exclusive culprit of facial aging and sagging is simplistic. There are no animal models for gravitational aging. There is tremendous individual variability in the degree of sagging, and age-related fibrosis (can anyone touch their toes like they used to?) may counteract increased laxity.

Indeed, sagging of the aging face may occur mostly as a result of changes in the fat compartments that are

coincident with chronological aging. Localized overabundance of fat may weigh down the tissue. Pendulous abdomens may hang due to excessive fat on the lowermost portion. Conversely, an area devoid of fat resembles a deflated balloon by inducing the downward displacement of facial skin. Inelastic recoil due to photodamage compounds this effect. If altered fat distribution underlies the differences between the young and old face, then a new model for the youthful countenance arises.

Facial Topography in the Young and Old

A young face has a smooth, ample distribution of fat. It resembles a continuous, "gently rolling plain" because the fat is evenly distributed. There is a forward projection with facial arcs highlighting specific areas and causing minimal shadow. In contrast, the aging face has "hills and valleys" producing deep shadows and irregular highlights. In thin individuals these "hills" of fat may be minor, but in most middle-aged adults the hills occur in a strip down the central face from midcheek to jowl, along the nasolabial

and labiomental folds. Fat pocketing can also be seen suborbitally on the lateral zygoma, submentally and along the neck platysmal bands. Since body fat rises with age, so does facial fat. "Valleys," in contrast, occur periorbitally and periorally, in the malar, buccal and temporal areas, and on the far lateral cheek. Fat loss manifests around the mandible, and throughout the forehead and scalp.

The Goal of Fat Rebalancing

One major goal of rejuvenation procedures is to rebalance fat and restore harmony to the face. This can be accomplished by microliposuction of the fatty "hills" and fat transfer to the sunken "valleys". Restoration of homogeneity to the facial structure reduces the sharp shadows associated with aging.

Initial Consultation

At the initial visit, the patient's face is compared to a photograph from 10-15 years ago. The dermatologic surgeon develops a "blueprint" of the areas to be augmented with fat and the areas to be suctioned. Dynamic changes in the underlying structure of the entire face are thus planned.

Principles of Facial Fat Rebalancing: A Step-by-Step Approach

1. Tumescent anesthesia (11 Lactated ringers solution, 50ml of 1% xylocaine, 1mg epinephrine, 12meq sodium bicarbonate) is locally infiltrated.
2. Fat is harvested from a donor site from which fat removal can induce cosmetic benefit. Buttock, outer thigh or abdomen fat has the greatest lipogenic activity.
3. Fat is harvested with minimal trauma.
4. Extraction is with an open tipped cannula attached to a 10cc syringe. The plunger is withdrawn 1cc at a time, generating small negative pressures. Suction machines are avoided.
5. The fat is sterilely centrifuged for 30 seconds at 3400 RPM.
6. The spun fat is transferred to 1cc syringes leaving the triglyceride layer.
7. Recipient sites receive facial blocks when possible to avoid distortion, then infiltration with 0.5% lidocaine with epinephrine.
8. Target areas are tumesced for hemostasis and anesthesia.
9. Entry sites on the face are made with an 18g Nacor[®]. Blunt-tipped 18g (or larger) cannulas are used.
10. Fat is transferred in less than 0.1cc aliquots, under low injection pressures.
11. Fat is deposited in thin strands during the withdrawal phase.
12. Fat is transferred starting submuscular when possible and weaving fat in a crosshatched 3-D design through the muscle to the subdermis. Periorbitally, fat is conservatively placed deep to the muscle.
13. Fat is only deposited in "virgin" tissue via fresh tunnels.
14. Fat is placed in and around folds to "suspend" skin. All facial areas are addressed.
15. Extra fat is stored in a freezer at -20°C and labeled in triplicate with name, date and SS#.
16. "Touch-ups" are performed every 4-8 weeks.
17. Frozen fat is rapidly thawed by placing syringes in an examination glove next to the patient's skin.
18. Fat from hypertrophic areas is suctioned by hand-held 10cc syringes and blunt-tipped 18-cannulas. Suction is staged for gradual skin contraction. Suction machines are avoided on the face.
19. Patients need 4-8 transfers +/- facial suction over a year for total correction.

Technique Dependence: Potential Pitfalls

Fat transfer is notoriously technique dependent. Common pitfalls are:

1. Underestimating the fat needed. Since most transfers place only 35cc of fat over the entire face, many transfers are required for remodeling.
2. Placing too much fat in one session. The fat may not survive, and the risk of lumps and cysts, especially around the eye, is increased.
3. Assuming incorrectly that the immediate post-treatment volume change is from fat. When blunt instruments are used, edema results. Patients usually like this swelling, because it allows them to "preview" the final results. However, this edema (lasting in a mild form for up to 2 months) will abate.
4. Filling the folds only. Folds in the face derive from "upstream" tissue shifts. For instance, the nasolabial folds are due to loss of central cheek mass. Cheek filling helps push up these folds.

5. Pouring off triglycerides before freezing, and slow “countertop” thawing of fat. Like glycerol, triglycerides have cryoprotective effects and should be left in before freezing¹. Rapid thawing is associated with ice crystal formation and cell death².

Utility of Frozen Fat

Using a patient’s own frozen fat obviates the need to resuction them. Frozen fat “takes” better than fresh fat.^{3,4,5} This may be from dehydration-induced stability of the adipocytes, or perhaps freezing “stresses” the cells into stability. In a rabbit model, previously suctioned frozen fat survived as well as fresh fat.⁶ Histologically, fat previously frozen for up to two years appears as morphologically intact as fresh fat.⁷ Additional evidence is the long-term volume change that the author has witnessed with frozen fat.

Long-term Outcomes

Gradual improvement occurs over a year, and the brief “down-time” accommodates active lifestyles. Patients “de-age” over time since the blueprint is fashioned on their younger selves. Each transfer/suction may make them look 2-5 years younger. Excellent fat retention results from small-volume, repeat injections and woven placement of fat grafts. Dynamic shifting of tissues is accomplished by global filling. Fat grafts remain anchored in fat and muscle.

There is controversy in the literature about the persistence of transplanted fat. Sadick⁸ found that in 5 of 6 patients, gluteal fat placed in the nasolabial folds could not be identified as such 4 months later. But Kaminer and Omura⁹ noted that secondary fibrosis rather than persistence of the fat per se may be responsible for the cosmetic benefits observed by many practitioners. They also reiterate that fat transplantation is a deceptively simple procedure with many parameters that can be altered and numerous operator-specific variations. In expert hands, fat rebalancing appears efficacious and is associated with high patient satisfaction.

Potential Complications

Possible complications include infection, graft absorption, bruising, swelling and under-correction. Over-correction

should not be seen, since the process is designed to be gradual and incremental.

Fat Rebalancing vs. Facelifting

Fat rebalancing can be done earlier than a facelift. Rather than inappropriately altering the patient’s appearance, fat makes the patient look like he or she used to look. Skeletonization or unnatural pulling is avoided. The fat procedure suits the 55 year-old who wants to look 40, or the 40 year-old who wants to look 30. In contrast to facelifts “tailoring” the skin around the aging framework, fat rebalancing replaces the lost framework so the skin can reassume its previous position. The patient can subsequently decide to modify the “blueprint.”

Maintenance and Repeat Treatment

Since patients will continue to age after the rebalancing treatments, they should consider maintenance visits 1-2 times a year. However, if they choose to stop treatments, they will age from that point on, the transplanted fat behaving like their own facial fat. Patients should maintain a consistent body weight for optimal post-operative results.

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Update on Drugs

Class	Name/Company	Approval Dates and Comments
Antihistamine	Cetirizine HCl <i>Zyrtec</i> [®] Pfizer	The US FDA approved pediatric use in November 2002, for this antihistamine. Zyrtec [®] is approved to treat year round-allergic rhinitis and chronic idiopathic urticaria in infants >6 months of age.
Atopic Dermatitis Agent	Pimecrolimus <i>Elidel</i> [®] Cream Novartis	By August 2002, 13 European countries gave their approval for this nonsteroid cream for the prevention of flare progression of atopic eczema in patients >2 years of age.
Immune Response Modifier	Imiquimod <i>Aldara</i> [®] Cream 3M	The US FDA approved a new pediatric indication for this immune response modifier in September 2002. This cream can now be used for the treatment of external genital and perianal warts and condyloma acuminata in patients >12 years of age.
Antiviral Agent	Valacyclovir HCl <i>Valtrex</i> [®] GlaxoSmithKline	The US FDA approved a new indication in September 2002. This antiviral product can now be used to treat cold sores (herpes labialis) in healthy adults at a dosage of 2gm po, b.i.d., for 1 day.

Drug News

Interstitial Granulomatous Dermatitis	<p>According to a recent article published in the <i>Journal of the American Academy of Dermatology</i>[*], Dermatologists should watch for signs of interstitial granulomatous dermatitis in their patients. Tomasini and Pippione suggest that patients who are found to have this condition on clinical examination may have an underlying systemic disorder. Their conclusion is based on a review of 17 patients, most of whom had rheumatoid polyarthralgias along with interstitial granulomatous dermatitis characterized by a diffuse infiltration of the interstitium of histiocytes with piecemeal fragmentation of collagen and formation of small granulomas around degenerative areas.</p> <p><small>*J Am Acad Dermatol 46(6):892-9 (2002 Jun).</small></p>
Atopic Allergies and Depression	<p>According to an article published in <i>Biological Psychiatry</i>[*], researchers from the University of Oulu in Finland report that women with IgE-mediated atopic allergies may have an increased risk for developing depression in early adulthood. Timonen, et al, used data from the Northern Finland 1966 Birth Cohort of newborns who were followed prospectively to age 31. Of the total cohort, 5428 individuals underwent skin tests for four of the most common allergens, i.e., cat, birch, timothy grass and dust mites. They also collected data on doctor-diagnosed lifetime depression from questionnaires. After adjusting for social class, mothers' parity, place of residence and psychiatric morbidity, analysis showed that the risk of developing depression when compared with nonatopic subjects was up to 1.8 times higher. The risk was 2.7 times higher in atopic women when compared with skin test negative female subjects without allergic symptoms. Corresponding associations were not found among the male subjects.</p> <p><small>*Biol Psychiatry 52:349-55 (2002 Aug).</small></p>

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