A SUPPLEMENT TO

JOURNAL OF DRUGS IN DERMATOLOGY

JDD

DRUGS • DEVICES • METHODS

Scientific Proceedings From Select Sessions at the 2010 Orlando Dermatology Aesthetic & Clinical (ODAC) Conference–Part II

ISSN: 1545 9616

August 2010 • Volume 9 • Issue 8 (Supplement)

JO0810

The supplement to the *Journal of Drugs in Dermatology* is based on the scientific proceedings from the 2010 Orlando Dermatology Aesthetic & Clinical (ODAC) conference, supported by educational grants and contributions from Abbott Laboratories, Allergan, Inc., Amgen, Inc., Centocor Ortho Biotech Services LLC, Galderma Laboratories L.P. and sanofi-aventis U.S.

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AUGUST 2010 VOLUME 9 ISSUE 8 (SUPPLEMENT)

ORIGINAL ARTICLES

Journal of Drugs in Dermatology (*JDD*) is indexed in MEDLINE®/PubMed® and is published monthly by
The Journal of Drugs in Dermatology
377 Park Avenue South, 6th Fl.,
New York, NY 10016
telephone: 212-213-5434
fax: 212-213-5435
www.JDDonline.com

Scalp Psoriasis

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ABSTRACT

Psoriasis is a chronic, debilitating disease that commonly involves the scalp. Despite a wide range of therapy options, scalp psoriasis remains difficult to treat, highlighting a long-standing unmet need for the safe and effective treatment of scalp psoriasis. Many topical therapies for scalp psoriasis are also difficult or unpleasant to apply, resulting in decreased adherence and efficacy. In brief, the high level of patient dissatisfaction with currently available treatments for psoriasis supports the need for new, effective and well-tolerated treatment options for scalp psoriasis. This article aims to review the efficacy and safety of new formulations and treatment options available to control scalp psoriasis. For example, a new formulation of calcipotriene/betamethasone scalp solution has a rapid onset of action with once daily dosing that improves compliance. The CalePso study examines the safety profile of otherwise established Clobetasol propionate (CP) shampoo 0.05%, and reports that CP shampoo is safe and efficacious in the long-term management of scalp psoriasis. A new foam formulation of coal tar is shown to be cosmetically acceptable and easier to apply.

INTRODUCTION

Psoriasis is a chronic debilitating disease of skin and joints that was noted to have a prevalence of 2.5 percent in Caucasians and 1.3 percent in African-Americans in a population-based study in the United States (U.S.).[1] In the Gelfand study,[1] approximately 50–80 percent of participants (79% according to van de Kerkhof et al.) have scalp involvement of psoriasis, which may occur in isolation or with any other form of psoriasis and still be termed scalp psoriasis.[2,3] The scalp is the most common site of disease involvement at onset and throughout the course of psoriasis. Although the area is small in relation to the body as a whole, it is disabling for the patient and causes many quality-of-life issues.

Scalp psoriasis presents as sharply demarcated plaques with silvery-white scaling. Sometimes the lesions involve forehead, the retroauricular area and back of neck, making the disease very apparent; and thus making it psychologically and socially very disturbing to patients.[4] At times, it is impossible to hide the scaling unless one wears a hat at all times or grows one's hair long. In a questionnaire-based study by Van de Kerkhof et al. in 1998, 57 percent of participants reported that scalp psoriasis is socially and psychologically distressing, with the most distressing symptoms being scaling (34%), itching (32%) and visibility (18%).[5] About 70 percent of participants with psoriasis complain of itching and/or skin pain and/or burning when the scalp is involved.[6]

Being a chronic disease, compliance in the treatment of psoriasis, especially scalp psoriasis, has always been of immense importance. Patients always expect a speedy and quick response, which is difficult to meet. Van de Kerkhof et al. showed that the most common reasons for non-compliance were desire of less frequent application (59%), treatment taking too much time (15%) and either treatment did not work or results were worse than expected (both at 10%).[5]

It is also important to determine the severity of scalp psoriasis. The Psoriasis Scalp Severity Index (PSSI)[7] is a modified PASI (Psoriasis Area Severity Index) which considers clinical signs and the scalp area only. Erythema, induration and scales are graded on a scale of 0 (absent) to 4 (very severe), summed up and then multiplied by the involved area of scalp which is graded on a scale of 1 to 6 (1=<10%, 2=10–29%, 3=30–49%, 4=50–69%, 5=70–89% and 6=90–100%). PSSI scores range from 0–72, just like PASI scores.

Scalp psoriasis is also very difficult to treat because the area does not represent the true burden of the patient's disease. Even if the whole scalp is involved, it is only five percent of the body surface area (BSA), which may not qualify the patient for the biologic agents that he or she may sometimes need. Scalp psoriasis can be treated in multiple ways. The treatment algorithm for the scalp is quite similar to that used for body psoriasis. The first line of treatment is topical—including tar and salicylic acids, which are messy, time consuming, odorous and may cause hair discoloration. Phototherapy, like skin psoriasis, would be the next option if topical therapy was not helpful because of poor response or severe disease. However, traditional light treatment units are vertical and emit light horizontally, making it impossible to treat the scalp. To overcome this, hand-held devices or units are available, but are inconvenient to use since the hand-held unit should be moved constantly over the scalp over a short period of time to avoid burning. Few patients with resistant scalp psoriasis will need systemic therapies such as methotrexate and acitretin, which may cause further hair loss, exacerbating the hair loss already known to be associated with scalp psoriasis.[4]

The optimal treatment of scalp psoriasis can be defined as an effective convenient application, with a cosmetically acceptable formulation, which will increase compliance and is safe for long-term use. Below the authors attempt to review the available medications and new formulations in terms of these criteria.

Taclonex Trial

Topical corticosteroids represent the most widely used treatment for scalp psoriasis. They have a rapid onset of action, however, and concerns about long-term cutaneous adverse effects and safety have always been an issue. To maximize safety and efficacy, corticosteroids are often combined with other topical agents. The vitamin D3 analogue calcipotriene is effective and well tolerated for the treatment of scalp psoriasis with proven superiority over the vehicle, but skin irritation can be a disadvantage.[8–10] Since 2001, the combination of calcipotriene with betamethasone dipropionate in an ointment formulation has become a well-established treatment for psoriasis vulgaris of the non-hairy skin.[11] Betamethasone provides rapid onset of action and counteracts the irritation of calcipotriol, while calcipotriol works as a steroid-sparing agent. Recently, calcipotriene/betamethasone has been made available in topical solution for scalp application.

A very large multicenter, randomized phase 3 trial was conducted in various centers in Canada, European Union (E.U.), United Kingdom (U.K.) and United States (U.S.) to evaluate calcipotriene/betamethasone scalp solution.[12] A total of 4,533 participants with scalp psoriasis were enrolled. Participants were at least 18 years old, with a clinical diagnosis of scalp psoriasis of >10 percent involvement and amenable to topical treatment with a maximum of 100 g of the scalp formulation per week. Following a washout period, participants were randomized to one of the following four comparison groups: calcipotriene/betamethasone scalp solution (n=541), calcipotriene in the same vehicle (n=272), betamethasone dipropionate in the same vehicle (n=556) and vehicle alone (n=136). All the subjects were evaluated at week 1, week 2, week 4 and week 8 on a six-point IGA scale ("very severe," "severe," "moderate," "mild," "very mild" and "clear or absence of disease"). The success was measured by either absence of disease or very mild disease.

At two weeks, 57.5 percent, and at eight weeks, 71.2 percent of participants treated with calcipotriene/betamethasone scalp solution achieved controlled disease status (i.e., absent or very mild disease). In contrast, 47.1 and 64 percent in the betamethasone group and 18.8 and 36.8 percent in calcipotriene group had achieved success respecitvely.

An open-label, 52-week safety and efficacy extension phase of this study was also conducted. The subjects were treated once daily with calcipotriene in vehicle (n=440) and calcipotriene/betamethasone scalp solution (n=429) on an as-needed basis. The end point was "satisfactorily controlled disease" which included absence of disease, very mild disease and mild disease.[13]

In 92.3 percent of the visits, of subjects treated with calcipotriene/betamethasone scalp solution achieved "satisfactorily controlled disease" level while the same number was 80 percent (58–78%) with the calcipotriene group. Hence, maintenance therapy with the two-compound scalp formulation may keep disease activity at a stable level while providing an acceptable safety profile when used as required.

Minimal and reversible adrenal suppression was observed in five out of 32 participants (16%) after four weeks of treatment with calcipotriene/betamethasone scalp solution, and in two out of 11 subjects (18%) who continued treatment for eight weeks. No clinically significant effects on serum or urinary calcium were noted in the 52-week study. It should be noted that most of the patients recruited for this study had extensive disease and were also using calcipotriene/betamethasone ointment for their non-scalp psoriasis.

In brief, calcipotriene/betamethasone scalp solution has a rapid onset of action and higher clearance with once-daily dosing, which improves patient convenience and compliance.[14–16] The safety and efficacy profile for up to 52 weeks is very assuring.

CalePso Study

Clobetasol propionate (CP) shampoo 0.05%, an efficacious and apparently safe treatment for scalp psoriasis, is approved by the U.S. Food and Drug Administration (FDA) for four weeks, but no long-term maintenance results were available. CalePso study was conducted in Canada to answer these questions.[17,18] The aim of this double-blind, randomized, placebo-controlled study was to determine if CP shampoo is suitable for long-term disease control. A total of 288 adult subjects with moderate-to-severe psoriasis (global severity score [GSS] of 3 or 4 on a scale of 0 [clear] to 5 [very severe]) were recruited. Initially, all the subjects entered an acute-phase, open-label phase of the study in which all were treated with 0.05% CP shampoo (contact time 15 minutes) daily for four weeks. Approximately 75 percent (78%) of subjects (217) with improvement to mild disease (GSS 2 or less) at four weeks, or to no disease (GSS 0) at two weeks, were rolled over to the maintenance phase of the study, which was placebo-controlled and double-blinded. Subjects were randomized to placebo or CP shampoo group, treated twice weekly and evaluated every four weeks for six months. Participants showing relapse (defined as GSS >2) were switched to daily clobetasol shampoo. If subjects relapsed twice in a row, they were withdrawn from the study. If symptoms diminished (GSS $\leq$2) after the first relapse, relapsed participants readopted the twice-weekly maintenance regimen.

After four weeks of open-label acute phase, 78 percent of the subjects had clear, very mild or mild (GSS <2) and 33 percent

of subjects has clear or very mild (GSS ≤1). Severe pruritus decreased from 75 to 27 percent in two weeks, suggesting a rapid onset of action of CP shampoo, which is required for good patient compliance. The safety profile was good with few adverse events reported of mild-to-moderate severity. Results are consistent with the U.S. pivotal trial studies (GSS 0 or 1 of 28–42%).

The maintenance phase was evaluated by relapse, which was defined as GSS of 3 or 4. The primary efficacy variable was time to first relapse, and the secondary efficacy variable was number of relapses during the six-month maintenance phase. It took a mean of 94 days for any subject to the first relapse in the clobetasol group while it took 57 days in the vehicle group (P<0.0001). Fifty percent of all subjects relapsed after 58 days of clobetasol shampoo versus 29 days of vehicle. Fifty percent of subjects with moderate psoriasis relapsed after 144 days in clobetasol group while 31 in vehicle group (P<0.0001). Fifty-seven percent of the clobetasol treated subjects had 0 or 1 relapse versus 30 percent in the vehicle group. Thirty-one percent in the clobetasol shampoo group had no relapse, versus 8 percent in the vehicle group. Two or three relapses were seen in 17 percent of clobetasol shampoo group, while 43 percent of vehicle group had two or three relapses over a period of six months. Over a period of seven months of study, no HPA axis suppression was reported in clobetasol group while, in contrast, one participant in the vehicle group was reported to have HPA axis suppression. There was no greater incidence of skin atrophy or telangiectasia in the clobetasol shampoo group compared with the vehicle group.

Coal Tar Revisited

Coal tar has been a part of traditional medicine for almost 2,000 years, and its first modern medical use was first documented in 1824. The Goeckerman regimen was introduced in 1925, a regimen in which coal tar is used in conjunction with UV light therapy. Coal tar has multiple mechanisms of action, including antimitotic, anti-inflammatory, antibacterial, antifungal, antipruritic and photo-sensitizing.[19] Although the frequency of its use has decreased due to availability of newer topical preparations, it still remains the mainstay of treatment for psoriasis in many parts of the world. The unpleasant smell, yellow staining and carcinogenic potential have been the major factors limiting the use of tars.

Coal tar is a monograph over-the-counter (OTC) drug (i.e., FDA has published a monograph on coal tar that specifies the kinds and amounts of ingredients, the directions for the drug's use, the conditions in which it may be used and the contraindications to its use). OTC coal tar is available in 0.5–5% strength and is useful in seborrheic dermatitis and dandruff as well other than psoriasis.

Liquid carbonis detergens (LCD) is a 10% coal tar solution that is equivalent to 2% coal tar. There is a study to compare psoriasis improvement rates in participants using 5% liquor carbonis detergens (LCD) (1% coal tar) in an emollient base with the emollient base vehicle alone, which was conducted in 1993.[20] Eighteen participants completed a randomized, bilaterally controlled, double-blind study. Emollient vehicle-treated plaques showed a mean improvement of 35.3 percent by four weeks of treatment, and LCD therapy produced a mean improvement of 48.7 percent, a difference which was statistically significant.

Tzaneva et al. showed in a pilot study that 1% coal tar preparation (Exorex) is similar in efficacy to calcipotriol in the treatment of psoriasis when treated for a short duration (eight weeks in this study).[21] Forty participants with chronic plaque type psoriasis were included in this randomized, observer-blind, split-body, intrapatient comparison trial. In each patient, two comparable target plaques were treated twice daily with a 1% coal tar preparation or calcipotriol cream and the response to treatment was evaluated at weeks 0, 2, 4, 6 and 8, determined by the psoriasis severity index (PSI). At termination of the trial, the mean±SD baseline PSI score of 9.2±1.5 was reduced to 3.0±2.9 by 1% coal tar preparation and to 2.8±2.7 by calcipotriol.

Many modifications have been made to tar preparations to increase their acceptability. Now new formulations are available and are being used for treatment of psoriasis. A new foam formulation is cosmetically acceptable, easier to apply, liked by the participants, has almost no smell (unlike old coal tar) and is greenish-yellowish in appearance but does not stain hairs. Other formulations are ointments, creams, lotions, gels and bath solutions.

Safety of coal tar has always been an important issue.[22] It is a polycyclic aromatic hydrocarbon which raises the possibility of carcinogenesis. There has not been any documented evidence of teratogenicity or carcinogenicity in humans, but these effects have been observed in animal and in vitro studies. Hence, long-term use with concentration over 5% of coal tar is not recommended. Proposition 65 (formally titled "The Safe Drinking Water and Toxic Enforcement Act of 1986" or "Prop 65") is a California law that has been in effect since 1986 to keep toxic substances that cause cancer and birth defects out of consumer products; coal tar is on this list.

There are some statistical analyses that suggest that the incidence of skin cancer is not significantly increased above the expected incidence for selected populations of the U.S.[23,24]

CONCLUSION

Scalp psoriasis is a common, symptomatic, highly visible and very distressing disorder. Affected patients have a high level of physical and psychosocial morbidity. There is an unmet need for safe, effective, long-term and easy-to-use topical treatments

for this condition. Mason et al. carried out a meta-analysis of antipsoriatic topical treatments and demonstrated that the only agents shown to be efficacious for the treatment of scalp psoriasis were potent topical corticosteroids and vitamin D3 analogues.[25] The use of traditional therapies for scalp psoriasis, such as coal tar and dithranol, and traditional vehicles, such as creams, gels and ointments, are self-limiting by high levels of unacceptability by patients. Formulation of topical treatment and once-a-day use is of utmost importance to achieve a high level of compliance and, therefore, treatment success. Recently formulated combination of calcipotriene/betamethasone dipropionate scalp solution, new information about the long-term safety of clobetasol shampoo and new coal tar foam have contributed to the advancement of scalp psoriasis treatment.

DISCLOSURES

Dr. Kircik is a consultant and investigator, and is on the Advisory Board, for Valeant Pharmaceuticals, Intl., Warner-Chilcott, Intendis, Amgen, Inc., and Galderma Laboratories, LP. He is an investigator, speaker, and is on the Advisory Board for Allergan, Inc. He is a speaker, investigator, consultant, and is on the Advisory Board for OrthoNeutrogena, SkinMedica, Inc., Stiefel Laboratories, Inc., and Connetics Corporation. He is an investigator, consultant and speaker for CollaGenex. He is a consultant and is on the Advisory Board for Colbar. He is a consultant for and stockholder in Johnson & Johnson. He is an investigator and speaker for Leo, PharmaDerm, UCB, and Asteilas Pharma US, Inc. He is an investigator and is on the Advisory Board for Nano Bio and Ferndale Laboratories, Inc. He is a speaker and is on the Advisory Board for Genentech, Inc. He is an investigator for GlaxoSmithKline, PLC, Health Point, LTD, Medicis Pharmaceutical Corp., Navartis AG, Nucryst Pharmaceuticals Corp., Obagi, QLT, Inc., Pfizer, Quatrix, TolerRx, Acambis, Asubio, Berlex Laboratories (Bayer HealthCare Pharmaceuticals), Biolife, Breckinridge Pharma, Centocor, Inc., Combinatrix, Coria, Dow Sciences and Dusa. He is a speaker for Innovail, 3M, Serono (Merck Serono International SA), Triax, Abbott Laboratories, and Dermik Laboratories. He is on the Advisory Board for Biogen-Idec.

Dr. Kumar has no relevant conflicts of interest to disclose.

REFERENCES

1. Gelfand, JM, Stern, RS, Nijsten, T, et al. The prevalence of psoriasis in African Americans: Results from a population-based study. *J Am Acad Dermatol*. 2005;52:23.
2. Papp K, Berth-Jones J, Kragballe K, et al. Scalp psoriasis: A review of current topical treatment options. *J Eur Acad Dermatol Venerol*. 2007;21(9):1151-1160.
3. van de Kerkhof PC, Steegers-Theunissen RP, Kuipers MV. Evaluation of topical drug treatment in psoriasis. *Dermatology*. 1998;197(1):31-36.
4. van de Kerkhof PC, Franssen ME. Psoriasis of the scalp. Diagnosis and management. *Am J Clin Dermatol*. 2001;2(3):159-165.
5. van de Kerkhof PC, de Hoop D, de Korte J, Kuipers MV. Scalp psoriasis, clinical presentations and therapeutic management. *Dermatology*. 1998;197(4):326-334. Erratum in: *Dermatology*. 1999;198(2):222.
6. CCF. Available at http://www.clevelandclinicmeded.com/medicalpubs/diseasemanagement/dermatology/psoriasis-papulosquamous-skin-disease/.
7. Thaçi D, Daiber W, Boehncke WH, Kaufmann R. Calcipotriol solution for the treatment of scalp psoriasis: Evaluation of efficacy, safety and acceptance in 3,396 participants. *Dermatology*. 2001;203(2):153-156.
8. Barnes L, Altmeyer P, Forstrom L, et al. Long-term treatment of psoriasis with calcipotriol scalp solution and cream. *Eur J Dermatol*. 2000; 10:199-204.
9. Thaci D, Daiber W, Boehncke WH, et al. Calcipotriol solution for the treatment of scalp psoriasis: Evaluation of efficacy, safety and acceptance in 3396 participants. *Dermatology*. 2001;203:153-156.
10. Green C, Ganpule M, Harris D, et al. Comparative effects of calcipotriol (MC903) solution and placebo (vehicle of MC903) in the treatment of psoriasis of the scalp. *Br J Dermatol*. 1994;130:483-487.
11. Douglas WS, Poulin Y, Decroix J, et al. A new calcipotriol/betamethasone formulation with rapid onset of action was superior to monotherapy with betamethasone dipropionate or calcipotriol in psoriasis vulgaris. *Acta Derm Venereol* (*Stockh*). 2002; 82:131-135.
12. Data on file. Warner Chilcott (US), LLC.
13. Luger TA, Cambazard F, Larsen FG, et al. A study of the safety and efficacy of calcipotriol and betamethasone dipropionate scalp formulation in the long-term management of scalp psoriasis. *Dermatology*. 2008;217:321-328.
14. Scott LJ, Dunn CJ, Goa KL, Calcipotriol ointment—A review of its use in the management of psoriasis. *Am J Clin Dermatol*. 2001;2(2):95-120.
15. Schimmer BP, Parker KL. ACTH; Adrenocortical Steroids and Their Synthetic Analogs. In: Brunton LL, Lazo JS, Parker KL, eds. Goodman and Gilman's: The Pharmacological Basis of Therapeutics. New York, NY: McGraw-Hill; 2006:1595-1600.
16. Taclonex Scalp® [package insert]. Rockaway, NJ: Warner Chilcott (US), LLC. 2008.
17. Poulin Y, Papp K, Bissonnette R, et al.; CalePso Study Team. Clobetasol propionate shampoo 0.05% is efficacious and safe for long-term control of scalp psoriasis. *Cutis*. 2010;85(1):43-50.
18. Tan J, Thomas R, Wang B, et al.; CalePso Study Team. Short-contact clobetasol propionate shampoo 0.05% improves quality of life in patients with scalp psoriasis. *Cutis*. 2009;83(3):157-164.
19. Thami GP, Sarkar R. Coal tar: Past, present and future. *Clin Exp Dermatol*. 2002;27(2):99-103.
20. Kanzler MH, Gorsulowsky DC. Efficacy of topical 5% liquor carbonis detergens vs. its emollient base in the treatment of psoriasis. *Br J Dermatol*. 1993;129(3):310-314.
21. Tzaneva S, Hönigsmann H, Tanew A. Observer-blind, randomized,

intrapatient comparison of a novel 1% coal tar preparation (Exorex) and calcipotriol cream in the treatment of plaque type psoriasis. *Br J Dermatol*. 2003;149(2):350-353.
22. Arnold WP. Tar. *Clin Dermatol*. 1997;15(5):739-744.
23. Pittelkow MR, Perry HO, Muller SA, et al. Skin cancer in participants with psoriasis treated with coal tar. A 25-year follow-up study. *Arch Dermatol*. 1981;117(8):465-468.
24. Maughan WZ, Muller SA, Perry HO, et al. Incidence of skin cancers in participants with atopic Dermatitis treated with coal tar. A 25-year follow-up study. *J Am Acad Dermatol*. 1980;3(6):612-615.
25. Mason J, Mason AR, Cork MJ. Topical preparations for the treatment of psoriasis: A systematic review. *Br J Dermatol*. 2002;146:351-364.

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How and When to Use Biologics in Psoriasis

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INTRODUCTION

Rationale for the Use of Biologics in Psoriasis

The term "biologics" encompasses all therapeutic and diagnostic agents that have been synthesized from living organisms. The Merriam-Webster's Medical Desk Dictionary defines a biologic as "a biological product (as a globulin, serum, vaccine, antitoxin or antigen) used in the prevention or treatment of disease." Biologics are designed to target a specific cell-surface receptor, cytokine or other molecule thought to be important in the pathogenesis of a particular disease. Specifically targeting these molecules can have significant clinical benefit and can help further characterize or solidify the potential relevance of certain cytokines in the disease.

In recent years, there has been significant advancement in the understanding of the pathogenesis of psoriasis and psoriatic arthritis, and, consequently, there has been a surge in the development and application of targeted biologic therapeutic agents for psoriasis and psoriatic arthritis. Key mediators in the pathophysiology of psoriasis include Th1 and Th17 cells and their respective proinflammatory cytokines, tumor necrosis factor alpha (TNF-α), interleukin-1 (IL-1), IL-6, IL8 and Il-12, and IL-23. Medications that block or inhibit these molecules have had a profound positive impact on patients with psoriasis and are collectively referred to as "the biologics."

An important question is: where does this newer class of medications fit into the classic treatment alogrithim for psoriasis? The traditional treatment paradigm for psoriasis follows a stepwise progression in which patients must fail a previous step of therapy in order to move up to the next-more aggressive treatment. In this model, systemic medications for a majority of psoriasis patients were a last resort if the patient has failed emollients, over-the-counter (OTC) products, topical glucocorticoids, vitamin D analogues or retinoids and phototherapy (UVB, UVA and/or excimer). With the expanding therapeutic armamentarium for psoriasis and the increasing awareness of the negative co-morbidities and risks associated with psoriasis, it seems prudent to rethink traditional treatment approaches.

More and more, systemic therapies are being initiated early in a patient's treatment course; yet, they are still typically reserved for patients with severe psoriasis. Plaque-type psoriasis, which encompasses 85 percent of cases, can be globally divided into three categories: mild, moderate or severe. Definitions of psoriasis severity have not been standardized, and conventional measures of disease severity are usually based solely on the percentage of body surface area affected. In this schema, >10 percent BSA corresponds to severe disease.[1,2] However, such measures of disease severity fail to consider a variety of factors. More recent disease severity qualifying schemes include quality of life measures, which provide a more comprehensive way to assess disease impact on patients.[3,4]

In an international consensus statement on biologic therapies for psoriasis published in the *British Journal of Dermatology* in 2004, several authors agreed that disease severity should be considered on a case-by-case basis.[5] This would allow for severe but localized involvement, disease that is localized to the face, palms, soles or genitals that can significantly impact the patient's quality of life to be considered severe enough to warrant systemic therapy. The most recent consensus statement from the American Academy of Dermatology (AAD) on psoriasis treatment echoes this statement and recommends that physicians take into account quality of life, co-morbid conditions, access to care and economic factors among others, prior to choosing an appropriate therapy for a patient.[6] Futhermore, it explicitly states that even mild disease can warrant systemic therapy if it is not responsive to topical therapy and/or it is causing significant disruption in daily life and/or employment. This is a clear shift from the traditional treatment paradigm and allows for a case-by-case approach to the treatment of psoriasis. Accordingly, systemic agents should be considered and discussed with the patient at the initial visit.

A growing body of evidence indicates that psoriasis is associated with significant medical co-morbidity in addition to the well-established negative psychosocial impact. For example, patients with severe psoriasis have a six-fold increase in risk of developing metabolic syndrome compared to the general population. Increased abdominal obesity and increasing BMI correlates with psoriasis severity.[7] Furthermore, psoriasis may be an independent risk factor for cardiovascular disease.[8] Compared to the general population, the 10-year risk of coronary heart disease and stroke were 28 and 11.8 percent greater, respectively, for psoriasis patients in one study.[9]

In terms of psychosocial morbidity, nearly half of patients with psoriasis would prefer to have a more "serious" medical condition than have psoriasis, 83 percent need to hide their psoriasis and avoid sports activities because of their psoriasis, 74 percent have lowered self-confidence, 46 percent were chronically depressed and 35 percent were inhibited in their sexual relationships.[10] Patients with psoriasis have an increased risk of

depression and use of selective serotonin reuptake inhibitors. Psychiatric morbidity is also present in children with psoriasis. In a study of 2,144 pediatric psoriasis patients (mean age 11.4 years), children with psoriasis were more likely to have a psychiatric disorder when compared to age matched controls.[11] Psoriasis has been shown to affect physical functioning more so than common serious medical conditions.[12]

Psoriasis can also permanently affect economic and social status. In one study, 23 percent of psoriasis patients reported that their condition affected the choice of their career.[10] More severe Psoriasis Area and Severity Index (PASI) and Dermatology Life Quality Index (DLQI) scores correlate with decreased work productivity. Patients with PASI and DLQI scores ≥20 were much more likely to be absent from work.[13] Psoriasis patients aged 29–34 have higher divorce rates, and overall have slightly higher divorced-marriage ratios than the general population.[14] Religious non-affiliation in psoriasis patients aged 29–31 is higher than in the general population. Divorce and religious non-affiliation are surrogate measures for social functioning. Overall DLQI over a lifetime or over the last year is worse than at a given point in time in patients with psoriasis.[15]

Despite these known psychosocial and medical co-morbidities, psoriasis patients are often frustrated and undertreated. Experienced psoriasis patients are often frustrated by the lack of efficacy and tediousness of applying topical medications and/or the frequent monitoring and visits associated with certain systemic medications and phototherapy. In a study of greater than 17,000 psoriasis patients, 78 percent expressed frustration with their current psoriasis treatment, and 32 percent felt that their treatment was not strong enough.[16] A study conducted by the National Psoriasis Foundation found that more than one-third of patients with severe disease did not receive any treatment.[17]

Newer data have shown that appropriately treating psoriasis has effects far beyond the skin. Treatment of psoriasis has been shown to decrease vascular diseases.[18] In a meta-analysis, patients treated with adalimunab (for Crohn's disease, psoriasis and psoriatic arthritis) lived longer than age- and disease-matched patients who were not treated with adalimumab.[19] Treatment with etanercept led to improvement in fatigue after 12 weeks of therapy.[20]

Considering the documented increased risk of cardiovascular co-morbities, the possible increased mortality,[21] the negative impact on quality of life and the knowledge that treatment may reduce or improve these negative associations, clinicians should adopt a more modern therapeutic approach that allows for more aggressive and earlier treatment. Treating psoriasis earlier can improve work productivity, improve psychosocial functioning and quality of life and possibly prolong life. The tools to improve skin related quality of life at any point in time are available to clinicians, and potential rapid improvement in quality of life should not be delayed. It is known that therapy improves psoriasis and quality of life as measured by the DLQI.[22,23] Considering that the DLQI measures only symptoms in the last week, it may be underestimating the larger negative impact on psychosocial functioning.

Discussion about systemic treatments for psoriasis including their risks and benefits should occur at the first visit. An ideal treatment is safe and effective, has low risk of systemic or organ toxicity, is well tolerated with minimal side effects, is convenient to use and provides lasting results. Current systemic agents indicated for the treatment of psoriasis include photochemotherapy; phototherapy; traditional systemic agents such as methotrexate, acitretin, cyclosporine and newer biologic agents, which will be discussed in detail below. Choice of systemic treatment should be individualized and take into account the patient's medical history, current medications, extent of psoriasis and co-morbidities. Another consideration before starting systemic therapy for psoriasis is the presence of psoriatic arthritis, which is a chronic autoimmune seronegative inflammatory arthritis that typically manifests as morning stiffness or persistent joint pain and/or swelling in the axial skeleton or the joints of the hands.

There are few head-to-head trials comparing the efficacy of the older systemic agents to the newer biologics for psoriasis. In one small study comparing adalimumab to methotrexate over a 16-week period, adalimumab showed superior efficacy, although the dose of methotrexate was not optimized in the study.[24] However, due to their target specificity, the biologics appeared to be less immunosuppressive compared to older agents that broadly suppress the immune system. In general, they are believed to have fewer side effects. Nonetheless, careful consideration to the patient's medical history before starting a biologic is essential.

Choosing which biologic to start is not standardized and should be considered on a case-by-case basis. The three main biologic strategies to treat psoriasis are T-cell inhibition, TNF-α blockade, and antagonism of IL-12/23. There is currently one T-cell antagonist, three TNF-α inhibitors (infliximab, adalimubab, etanercept) and one IL-12/23 inhibitors approved by the U.S. Food and Drug Administration (FDA). Briakinumab (ABT-874, Abbot), an IL-12/23 antagonist that is effective for psoriasis, is still undergoing clinical trials and doses are not yet known. Each treatment has advantages and disadvantages, and there are clear differences in efficacy. Efalizumab was previously approved for the treatment of moderate-to-severe psoriasis in Europe and the U.S., but it has been withdrawn from both markets due to its increase risk of progressive multifocal leukoencephalopathy (PML). Below, the authors will discuss each of the five biologic treatments approved for the treatment of

psoriasis and provide insight on how and when to use them in patients with psoriasis.

Alefacept

In January 2003, Alefacept (Amevive Biogen) was the first biologic agent to be approved by the FDA for the treatment of psoriasis. Alefacept is a recombinant dimeric fusion protein made up of the terminal portion of the leukocyte function antigen-3 (LFA-3) that binds to extracellular human CD2 and the Fc portion of human immunoglobulin IgG1. It competitively inhibits the interaction between LFA-3 on an antigen-presenting cell and the CD2 molecule on subsets of T lymphocytes (primarily CD45RO+). As a result, activation and proliferation of memory effector (CD45RO+ T cells) T lymphocytes, which make up more than 75 percent of the T lymphocytes in psoriatic plaques, are inhibited which decreases the number of pathogenic T cells. Alefacept also induces apoptosis of T cells, which further reduces the number of pathogenic T cells. Reduced CD45RO+ T lymphocyte counts in patients receiving alefacept have correlated with significant clinical improvement.[25,26]

Alefacept is administered by intramuscular (IM) injection, once a week for 12 weeks, followed by a repeat round of treatment after 12 weeks if there is clinical improvement. Clinical benefits persist even after treatment is stopped. Treatment with IV and IM alefacept was associated with a median duration of off-treatment response of 209–219 days.[27]

Although alefacept is the only biologic agent without a box warning and has the longest time on the market for treatment of psoriasis, its efficacy is far less in comparison to the other biologic therapies. In the initial trial, 21 percent of patients achieved a PASI 75 at week 12. [28] Of the patients who did not achieve PASI 75 with the initial course of alefacept, 13 percent did demonstrate this level of efficacy with a second course, and 35 percent reached PASI 50 with a second course.[29]

In seven years of use, there have been no serious safety concerns. In clinical trials and in post-marketing use, there has been no increased risk of infection or malignancy. In an analysis of 1,869 patients treated with up to nine courses of alefacept over a five-year period, less than 1 percent of patients developed a serious infection during a course of therapy. There were no opportunistic infections or deaths, and <2.5 percent of patients developed anti-alefacept antibodies.[30] In patients who respond, effects can last eight to 10 months, and a second course can improve response rates.

Alefacept may be a good choice in patients where TNF-α antagoinists are contraindicated and also may appeal to patients who only want limited treatment. Disadvantages are its delayed response; with a maximun response seen 16 weeks after starting the medication. There is no way of predicting who will respond, so patients must commit to 16 weeks before determining if the treatment was beneficial or if they will need an alternative medication. In addition, while there is some literature that the combination of alefacept and methotrexate is beneficial for psoriatic arthritis, alefacept alone is not very effective against psoriatic arthritis.[31] Side effects unique to alefacept include decreased CD4 counts and the need for monitoring patients' levels every two weeks during treatment. There are not much data in terms of its effects on co-morbidities associated with psoriasis. Relative to some of the other biologics, there is less overall power in the safety data because of the smaller number of total users.

Alefacept should not be used in patients with lower than normal CD4 T-lymphocyte counts or patients who are infected with HIV because it can accelerate the disease. Alefacept is pregnancy catergory B.

TNF-α Inhibitors

TNF-α is a major cytokine produced by T helper 1 (Th1) cells, antigen presenting cells, and keratinocytes. Psoriatic skin has increased levels of TNF-α compared to non-involved skin and increased lesion and serum TNF-α levels correlate to severity of disease. It is still not entirely clear how blockage of TNF-α leads to improvement in psoriasis, but recent data shows that response to therapy is linked to suppression of IL-17 signaling.[32] TNF-α potentiates the Th1 response in inflammatory reactions. It exists as a membrane-bound protein that can be cleaved by a TNF-α converting enzyme to its more potent, soluble form. TNF-α binds to two TNF-α receptors (TNF-α R), p55 and p75 that is internalized into the cell and can activate transcription factors such as NFkB.[33] There are currently three TNF-α antagonists approved for psoriasis, and these will be discussed below.

Etanercept

Etanercept (Enbrel, Amgen, Thousand Oaks, CA) is a dimeric, fully human fusion protein consisting of two ligand binding domains of the p75 TNF-α receptor fused to the Fc portion of human IgG1, and it binds both soluble and membrane-bound TNF-α, thus preventing the cytokine from binding to any cell surface receptors.

Etanercept is administered as a subcutaneous (SC) injection, and recommended dosing is 50 mg twice weekly for three months, then 50 mg weekly. However, variable dosing regimens exist, such as 25–50 mg once weekly, or 25–50 mg twice weekly.

Several large, randomized, double-blind, placebo-contolled studies have evaluated the efficacy of etanercept for psoriasis. In a phase 3 multi-center, double-blind, placebo-controlled study of 583 patients with moderate-to-severe psoriasis, PASI 75 at 12 weeks was 49 percent for patients receiving 50 mg BIW

(twice-weekly), 34 percent for patients getting 25 mg BIW and 3 percent for placebo.[34]

In one study, the PASI 75 at 12 weeks of therapy was 4 percent for placebo, 14 percent for patients treated with 25 mg once weekly, 34 percent in the 25 mg twice-weekly group and 49 percent in the 50 mg twice-weekly group. At 24 weeks, the response rates increased to 25 percent, 44 percent and 59 percent in the low, middle and high dose groups respectively.[35] With extended treatment 63 percent of patients maintain PASI 75 at week 48, and at week 96, 52 percent maintain this level of response.

Etanercept has the advantage of long-standing use for several indications including psoriasis. It has been used in patients with rheumatoid arthritis (RA) since 1998, and long-term safety studies in these patients have revealed no cumulative toxicity.[36] A 96-week open label extension study of a phase 3 placebo-controlled trial that compared etanercept 50 mg BIW to placebo revealed that no patients developed neutralizing antibodies, and that there was no increased safety risks compared to taking enbrel once a week.[37]

Side effects of etanercept use include mild pruritic injection site reactions and rare cases of serious infections. Additionally, as with the other TNF-α antagonists cases of drug-induced lupus, multiple sclerosis and exacerbation and/or new onset or worsening of pre-existing congestive heart failure (CHF) have been reported.

Adalimumab

Adalimumab (Humira, Abbott, Princeton, NJ) is a fully human IgG1 recombinant antibody to TNF-α that can lyse cells that express TNF-α on their surface. It was approved for the treatment of moderate-to-severe psoriasis in January 2008. Adalimumab is administered as a subcutaneous injection and for psoriasis; it is administered as an 80-mg injection on day 1 followed by 40 mg subcutaneously on day 8, then 40 mg SC every other week. Alternatively, it can be dosed 40 mg every other week starting on day 1.

In a randomized, multi-center, double-blinded placebo-controlled trial of 147 patients with moderate-to-severe psoriasis, PASI 75 at 12 weeks was 53 percent for patients receiving 80 mg loading doses at week 0 and 40 mg every other week beginning at week 1, and 80 percent for patients who received 80 mg loading dose at weeks 0 and 1 and then 40 mg every other week beginning at week 2, compared to 4 percent for placebo.[38] In a phase 3 clinical trial, 71 percent of patients achieved a PASI 75 at week 16, and 64 percent maintained PASI 75 at 24 weeks and 58 percent maintained this level of response at 60 weeks.[39,40] In another recent large clinical trial showed that if treatment with adalimumab is discontinued once PASI 75 is achieved, the majority of patients lose this response in four to five months.[41] Also, PASI 75 response in a 120-week adalimumab study with ITT analyses was 41 percent. However, PASI 75 response in the same study was 78 percent with as-treated analyses.It is important to realize the differences in PASI 75 response between the two analyses (Figure 1).

It also appears that heavier patients respond less favorably to adalimumab. Sixty-one percent of patients weighing >105 kg achieved a PASI 75 at week 16 compared to 74.1 percent of patients who weighed less than 77.6 kg.[42]

Anti-adalimumab Antibodies

A recent publication by Lecluse et al. clearly demonstrated the there is a direct correlation between human antibody formation to adalimumab and lack of response.

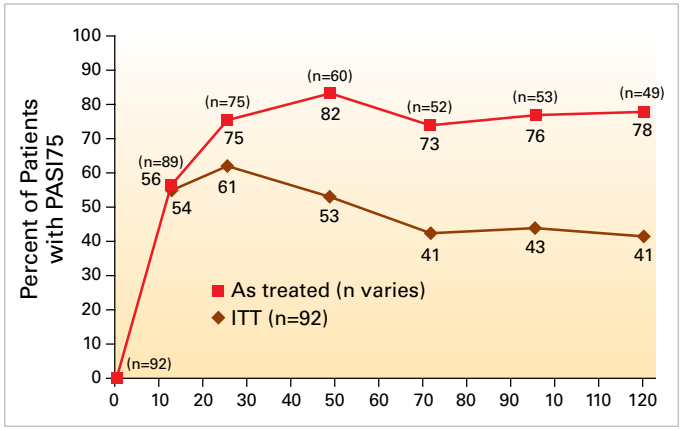
A cohort of 29 consecutive patients were started on adalimumab at two academic centers in the Netherlands for 124 weeks. Anti-adalimumab antibody levels were measured by a radioimmunoassay using a technique developed by Sanquin research. Patients were classified at week 12 and week 24 as non-responders if PASI <50, moderate responders if PASI 50–75, good responders PASI >75. Response rates to adalimumab in this study was 32 percent at week 12 and 34 percent at week 24, which is different than phase 3 adalimumab trials (PASI 75 at week 12 was 53% for phase 3 trials).

At week 24, 45 percent of the patients developed antibodies to adalimumab. Differences in response rates among patients with low, high and no titers of antibodies were significant at weeks 12 and 24 (P=0.04, P<0.001, respectively). [43]

These findings also confirm previously published studies that show immunogenicity negatively influencing the outcome of adalimumab treatment in Crohn's disease.[44]

Originally, 8.8 percent of the subjects in REVEAL study had also detectable anti-adalimumab antibodies through a 52-week

FIGURE 1. Adalimumab and long-term data.



treatment period. Forty-three percent of those subjects lost an adequate response.[40]

Adalimumab product monograph also informs about adalimumab antibody association with increased clearance and reduced efficacy of adalimumab and methorexate-reducing adalimumab apparent clearance after single and multiple doses by 29 percent and 44 percent, respectively, in patients with rheumatoid arthritis.[45]

Advantages to adalimumab are the less frequent dosing and the slightly better efficacy. Because it is the newest of the anti-TNF-α medications for psoriasis, safety data is limited relative to etanercept and infliximab. Common adverse events in patients treated with adalimumab for psoriasis include upper respiratory tract infections, headaches and injection site reactions (in up to 15%).[46] In addition, safety precautions common to all the TNF-α antagonists will be discussed below.

Infliximab

Infliximab (Remicaide, Centocor, Horsham, PA) is a chimeric (25% mouse and 75% human) monoclonal IgG1 antibody to TNF-α. It neutralizes soluble TNF-α and blocks membrane-bound TNF-α. Infliximab is indicated for the treatment of rheumatoid arthritis, psoriatic arthritis, Crohn's disease, ulcerative colitis, ankylosing spondylitis and plaque-type psoriasis and is administered via IV infusion at specialized infusion centers. For psoriasis, dose is weight-based, and, typically, a dose of 5 mg/kg is given at weeks 0, 2 and 6, and then every eight weeks thereafter.

Of the three TNF-α antagonists approved for psoriasis, infliximab has the fastest onset of action and achieves PASI 75 in the greatest number of patients. In an early study of patients with moderate-to-severe psoriasis, 87.9 percent of patients who received 5 mg/kg versus 71.7 percent of patients who received 3 mg/kg of infliximab achieved PASI 75 at week 10, compared with 5.9 percent for the placebo group.[46] In two large phase 3 trials, 81 percent of patients achieved PASI 75 at week 10.[47] At week 50, 55–61 percent maintained PASI 75 on infliximab 5 mg/kg.[48] Infliximab has also been effective for pustular psoriasis.[49]

Loss of efficacy in a proportion of patients on infliximab over time is probably due to the development of neutralizing antibodies. Loss of response is also believed to be related to trough level. If the trough level at time of the next infusion is <0.1 mg/ml one can predict that the response will be lost, if it is >10 mg/ml, the response will be maintained. Methotrexate can delay clearance of infliximab and can help counteract antibody formation.[50] Increased frequency of infusions rather than increased dose of infliximab may also help maintain response.

The safety data on infliximab is largely extrapolated from the rheumatoid arthritis patients in whom treatment with infliximab has been well established and is well tolerated. In a study of 1373 patients treated with infliximab for psoriasis, rates of infection and mortality were compared to the general population over the course of one year. Patients treated with infliximab did not have higher rates of mortality, hospitalization, serious infections (except reactivation of tuberculosis [TB]) or malignancy when compared to the general population.[51] Only rates of reactivation of TB were higher in the infliximab treated patients.

Although infliximab may be advantageous in heavier patients because the dose is weight-based and in those with severe disease because it works quickly, the drawbacks include a high rate of neutralizing antibody formation (bind to the mouse-derived portion of the molecule), which leads to loss of efficacy. There is also a need to have access to an infusion center to receive the medication, which is inconvenient and adds to the overall cost of the medication.

In addition, 3–22 percent of patients receiving infliximab for psoriasis experience an infusion reaction, which is characterized by flushing, chest tightness, shortness of breath, headache, hypo/hypertension, nausea and sweating.[52] Most of these reactions occur within 24 hours and can be treated by slowing the rate of the infusion and the use of acetaminophen and antihistamines.[53] Few infusion reactions are severe with symptoms of anaphylaxis or are delayed reactions that occur between 24 hours and 14 days after an infusion (usually five to seven days).[54] Up to 40 percent of patients on infliximab experience increased liver enzymes. In the clinical trials with infliximab, six percent had elevated alanine aminotranserase of greater than 150, and two percent had elevated aspartate aminotransferase greater than 150. In 2004, the FDA issued a warning about hepatic disease including severe hepatic failure with infliximab therapy. There have been six reported cases of hepatosplenic T-cell lymphoma, but all six were patients with Crohn's disease who were also on thiopurines and other immunsuppressive medications. As with patients receiving other TNF-α antagonists, patients on infliximab have an increased increase risk of herpes zoster reactivation.

Safety Precautions for the TNF-α Antagonists

In addition to the specific side effects unique to each of the TNF-α antagonists, there are several safety considerations common to all, including serious infections, opportunistic infections such as reactivation of latent tuberculosis (TB), malignancies, neurologic/demyelinating diseases and drug-induced lupus-like syndromes. Most of these safety issues are being extrapolated from data that was gathered from patients who have been treated with the TNF-α inhibitors for rheumatoid arthritis and inflammatory bowel disease and thus may overestimate the potential risk of these agents when used as single agents for psoriasis.

While mild upper respiratory infections are the most common, more serious opportunistic infections have been

reported with all three agents but more commonly with infliximab and adalimumab. Specifically, mycobacterium tuberculosis (TB) and reactivation of hepatitis B have been documented in patients treated with all 3 anti TNF-α, although less so with etanercept.[55]

All patients who will be treated with anti-TNF treatment should undergo testing for hepatitis B, including HBcAb, and have close follow-up with liver function testing (LFT) during therapy.[56]

On the contrary, TNF-α may be involved in the pathogenesis of hepatitis c and several studies have shown that anti-TNF-α therapy is safe in patients with hepatitis C infection.[57,58] Thus, TNF-α inhibitors are generally contraindicated in patients with hepatitis B and active TB.

Peripheral and central demyelinating disorders, including multiple sclerosis (MS), have been reported to develop and/or worsen while on TNF-α inhibitors.[59] There are anecdotal reports of the development of demyelinating disorders while on TNF-α inhibitors, resolution with discontinuation and recurrence with re-introduction of the medication.[60] In addition, first-degree relatives of patients with MS have an increased risk of MS, and thus TNF-α antagonists should not be used in patients with a personal history or family history of a first-degree relative with a demyelinating condition. Patients on therapy should be screened for the development of neurologic symptoms at each follow up visit.

The development of lymphoproliferative malignancies secondary to TNF-α inhibitors is a controversial issue and has arisen from anecdotal cases of lymphomas developing while on therapy.[61] The risk may be independent of treatment. In an epidemiologic study of patients with severe psoriasis using a Medicaid database, Margolis et al. found that patients with severe psoriasis had an eight-fold increased risk of developing lymphoproliferative malignancies and two- to four-fold increased risk of skin malignancies regardless of treatment.[62] In addition, a large cohort of rheumatoid arthritis patients showed no relative increased risk of malignancy for patients who were on etanercept, infliximab or adalimunab. When adjusted for duration of exposure, infliximab was associated with an increased risk; however, these patients may have had more severe disease and been on other immunosuppressive medications.[63] A critical review of clinical evidence concluded that the overall risk of all malignancies including lymphoma was not increased over baseline levels in patients with rheumatoid arthritis being treated with tumor necrosis factor (TNF)-α inhibitors. Furthermore, a thorough review of patients on biologics for psoriasis showed that there was insufficient evidence to firmly establish a causal relationship.[64] Nonetheless, one must use caution and elicit a careful history of malignancy prior to treatment with a TNF-α inhibitor.

Heart failure is another controversial issue, as studies have shown conflicting results. Current recommendations state that TNF-α inhibitors should be avoided in patients with severe congestive heart failure (CHF) (class 2 or 4) and those with mild CHF should stop therapy with TNF-α inhibitors if there are new onset symptoms of heart failure or if there is worsening of pre-existing CHF.[65]

Anti-nuclear antibodies can develop in patients taking any of the three TNF-α inhibitors, but this is nonspecific, does not correlate with active lupus and does not necessitate drug cessation. There are only a few cases of true systemic lupus occurring while on TNF-α inhibitors. However, clinicians should be aware of this entity and work up patients with clinical symptoms of lupus.[65]

Relative contraindications for anti-TNF-α therapy are unstable diabetes mellitus (DM), chronic infections, malignancy and long-term PUVA.

IL-12/23 Inhibitors

Interleukins 12 and 23 are believed to play an important role in the pathophysiology of psoriasis. IL-12 is important in the differentiation of helper T cells into Th1 cells in lymph nodes. IL-23 influences the activation and proliferation of Th17 memory T cells. Both are secreted by activated dendritic cells in the skin. Both these cytokines are increased in psoriasis plaques compared to non-lesional skin.[66] Thus, molecules that specifically interfere with these cytokines have been and are currently being developed for the treatment of psoriasis.

Ustekinumab

Ustekinumab (CNTO 1275, Centocor Ortho Biotech, Horsham, PA) is a fully human monoclonal IgG1 antibody that binds with high affinity to the shared p40 subunits of IL-12 and IL-23 and neutralizes their activity. It was approved for moderate-to-severe psoriasis in 2009. Currently, ustekinumab is administered by injection in a physician's office at weeks 0 and 4, and then every 12 weeks. Pharmacokinetic studies showed decreased blood levels with increased body weight and thus dosing for ustekinumab is weight-based.[67] Patients who weigh >220 pounds (100 kg) receive 90 mg, those who weigh less than 220 pounds receive 45 mg on week 0, a second injection four weeks later and then one injection every 12 weeks.

The initial studies with ustekinumab showed efficacy after a single injection. With one injection of 45 mg, 50 percent of patients reached PASI 75 and with one injection of 90 mg, 59 percent reached PASI 75.[68] Later, two large phase 3 multi-center, double-blinded placebo controlled trials confirmed the excellent response to ustekinumab using the currently indicated dosing regimen (PHOENIX 1 and 2). At week 12, 67 percent of patients with moderate-to-severe psoriasis on 45 mg and 66 percent on 90 mg achieved PASI 75 compared to 3 percent in placebo.[69]

This response was maintained; after four injections of 45 or 90 mg, 71 and 79 percent respectively achieved PASI 75. In the second phase 3 study, patients were randomly assigned to receive 45 or 90 mg at weeks 0 and 4, and then every 12 weeks, or placebo. Patients who achieved ≥50 percent but less than 75 percent improvement from baseline in PASI were labeled partial responders and were then re-randomized at week 28 to either continue dosing at every 12 weeks or escalate to dosing every eight weeks. At week 12, 66.7 percent of patients receiving 45 mg and 75.7 percent receiving 90 mg achieved a PASI 75. At week 52, 68.8 percent of partial responders who had intensification of dosing to every eight weeks compared to 33.3 percent of partial responders who were kept on an every 12 week dosing regimen achieved PASI 75.[70]

Clinical responses to ustekinumab were apparent as early as week 2, with maximum response rates seen after about six months of treatment. In addition, patients who were withdrawn from ustekinumab experienced gradual recurrence of their psoriasis. Ustekinumab was also shown to significantly benefit quality of life as measured by the DLQI.[71]

Common side effects (occurring in >3% of patients) were nasopharyngitis, upper respiratory infections, headaches and fatigue; there were no active TB cases. There was one report of reversible posterior leukoencephalopathy in a patient receiving ustekinumab. Overall rates and types of adverse events and lab abnormalities were comparable between patients receiving ustekinumab or placebo during the placebo-controlled phases in both trials.[72] Increased rates of cardiovascular events were observed in the study by Kreuger et al. In a controlled period of ustekinumab trials, there were a total of five major cardiovascular events in ustekinumab arms, versus none in placebo arms. In three years, there were a total of 18 major cardiovascular events in ustekinumab arms[70] In a briakinumab study (ABT-874 Abbot), during the induction phase, there were five major cardiovascular events in active arms versus none in placebo, and, during the maintenance phase, there were two major cardiovascular events in active arms versus none in placebo.[73] Therefore, major cardiovascular events associated with IL12-23 antagonists may require caution.

The advantages of using ustekinumab are the convenience of the infrequent dosing, which improves adherence and patient satisfaction. Drawbacks include limited safety data up to three years, and thus the long-term safety and cumulative toxicity is unknown.

Similar to the TNF-α antagonists, patients taking ustekinumab should avoid live vaccines while on treatment. Based on patients who have genetic deficiencies in IL-12 and IL-23, there is a potential risk of malignancy and increased opportunistic infections.

Efficacy

Although studies of efficacy of each biologic uses PASI 75 as a common outcome measure making it easy to compare efficacy, there are differences in study design and data analysis that prevent a truly equal comparison. More head-to-head trials comparing one biologic to another or to other systemic agents are needed. In a recent study, two doses of either 45 or 90 mg of ustekinumab (at day 1 and week 4) was compared to 50 mg SQ twice weekly of etanercept and found superior efficacy of ustekinumab at 12 weeks. Seventy percent of patients who received 45 mg and 75 percent of those who received 90 mg of ustekinumab achieved a PASI versus 55 percent of patients who were treated with etanercept. However, there were three non-melanoma skin cancers and one breast cancer in the ustekinumab arm during the first 12-week period, versus none in the etanercept arm. At the end of the study, there were a total of nine non-melanoma skin cacners, one from cross-over arms and eight from ustekinumab arms.[74]

Baseline Evaluation, Monitoring and Vaccines During Therapy

There are no evidence-based guidelines for how and when to perform baseline evaluation, monitoring studies or administer vaccinations while patients are on biologic treatment for psoriasis. In response to this, the medical board of the national psoriasis foundation surveyed its members on their practices and reviewed the medical literature (gastroenterology, rheumatology, dermatology and transplant) and data presented at meetings and issued a consensus statement to serve as a guideline before actual guidelines are established.[74] It is important for patients to understand that psoriasis is a chronic disease, and, similar to other chronic diseases, treatment may be indefinite and thus need for monitoring is important.

Baseline Studies

Prior to starting biologics a thorough medical history that includes the presence of diabetes, congestive heart failure (CHF), a demyelinating disorder (multiple sclerosis or other), history of lupus, history of malignancies (especially skin, prostate, breast and lymphoma), current or recurrent infections, history of immunodeficiency, history of anemia or thrombocytopenia is necessary. History of tuberculosis or exposure to tuberculosis should be noted. Family history of neurologic and autoimmune diseases should be elicited. Review of systems at the baseline visit should include screening for symptoms of CHF, neurologic disease and chronic infections. Patients should also have a total body skin exam not only to document the baseline severity of the patient's psoriasis but also to examine for any cutaneous malignancies.

At baseline and at each subsequent visit, patients should be asked about symptoms of psoriatic arthritis including morning stiffness, joint pain and/or swelling. If joint symptoms are pres-

ent, baseline joint x-rays and consultation with a rheumatologist are helpful. Psoriatic arthritis is an inflammatory seronegative spondyloarthropathy that is present in a proportion of patients with psoriasis (range 6–42%) and usually presents on average 10 years after the onset of skin disease.[75] If untreated, psoriatic arthritis can lead to joint destruction and significant impairment and disability. Thus, early identification and aggressive treatment is essential.

Patients who are being considered for treatment with any of the biologics are suggested to have a complete blood count, comprehensive metabolic profile, and testing for human immunodeficiency virus (HIV) and hepatitis B and C at baseline. Anti-nuclear antibodies (ANA) can be checked at baseline but is not absolutely necessary. Nonetheless, patients may develop ANA antibodies while on treatment with the anti-TNF-α agents and some clinicians would prefer to have baseline testing. The development of ANA does not require interruption of therapy. In addition, because alefacept can selectively decrease CD4 counts, a T-cell profile should be obtained if the patient will be starting alefacept.

Baseline testing for tuberculosis (TB) with the protein purified derivative (PPD) also called the tuberculin skin test (TST) prior to starting treatment is advocated by the centers for disease control (CDC) and is listed on the package inserts for adalimumab, infliximab and etanercept. If TB skin test is positive, a chest radiograph is required to rule out active infection. A patient with a positive PPD should be referred to the appropriate specialist for treatment of latent TB. For patients who have positive PPD related to BCG vaccination or those on immunosuppressants, the quantiferon test can be helpful in detecting the presence of TB.[76]

Monitoring While on Therapy

At each follow-up visit, patients on therapy with a biologic should be screened for interim and current infections, the development of joint symptoms, morning stiffness and injection site reactions. Medication-specific side effects such as symptoms of CHF (weight gain, fatigue) and of demyelinating disorders (numbness, tingling of extremities, double vision, blurry vision, etc.) for the TNF-α inhibitors should also be documented at each visit.

Repeat CBCs should be performed every two to six months in patients taking adalimumab, etanercept or infliximab. With alefacept, which can lower CD4 counts, a T-cell profile should be monitored every two weeks during the 12-week course of alefacept, and the dose should be held or delayed if CD4+ counts decrease below 250 cells/uL. Some clinicians discontinue monitoring CD4 levels after two normal levels.

Although hepatoxicity appears to be a concern only with infliximab, the majority of experts surveyed check chemistries, including liver function tests at a minimum of six-month intervals. Treatment is held if transaminases rise above (greater than or equal to) five times the upper limit of normal. For alefacept, baseline chemistries should be repeated at the start of each course of therapy.

Infection with *Mycobacterium tuberculosis* has been demonstrated in patients treated with infliximab, adalimumab and etanercept as well as methotrexate and cyclosporine. An annual PPD is advisable for patients on any long-term systemic immunosuppressive treatment for psoriasis.

Vaccines

Live vaccines pose a risk of infection in patients who are immunosuppressed on any of the biologics for psoriasis and should be avoided while on therapy. Vaccination during treatment with a biologic may also result in a decreased antibody response and lack of efficacy. When practical, routine age-appropriate standard vaccinations should be given prior to starting therapy with a biologic as is done in patients prior to organ transplant that will require life-long immunosuppression.[77] These usually include the pneumococcal vaccine, hepatitis A and B vaccines and the diphtheria-tetanus booster. However, annual vaccination with the inactivated influenza vaccine is recommended for patients on any biologic therapy.

Combination Therapies

Combination therapies can improve outcomes while decreasing toxicity of each individual agent. There is extensive literature on the safety and efficacy of the combination of methotrexate and anti-TNF-α therapy in the treatment of psoriatic arthritis.[78] For psoriasis, the addition of a biologic can help lower the dose of methotrexate and ultimately its cumulative toxicity. In addition some experts believe the addition of methotrexate to TNF-α inhibitors can improve efficacy.

Ultraviolet light therapy is a long-standing effective treatment for psoriasis that is often limited because of the requirement for two to three times weekly office visits. In a recent study, the combination of etanercept 50 mg SC BIW and narrow-band ultraviolet light B (NB-UVB) three times weekly was evaluated for patients with moderate-to-severe plaque psoriasis for 12 weeks. In this study, 26.0 percent achieved PASI 100, 58.1 percent achieved PASI 90 and 84.9 percent of patients achieved PASI 75 at week 12 which was higher than in studies of etanercept alone.[79] Mean improvement from baseline in DLQI was 84.4 percent. No serious adverse events were noted. Although these results are promising, it is unknown if this response will last long-term.

One study combined etanercept 25 mg twice weekly or once weekly and acitretin (0.4 mg/kg daily) in chronic plaque psoriasis and found that etanercept 25 mg once weekly with acitretin was as effective as etanercept 25 mg twice weekly.[80]

Recent data has shown that for patients who do not respond to an initial course of treatment with any one of the above biologics, trial with another agent, in the same or another class, may be effective. In 50 patients who were refractory to etanercept 50 mg BIW at week 12 (still had a PGA score of >3) were crossed over to receive ustekinumab at weeks 16 and 20. Of the etanercept non-responders, 40.4 percent achieved PASI 75 at week 12 on ustekinumab.[81] Similarly adalimumab was effective in a proportion of etanercpt non-responders after 24 weeks of use.[82] In another study 52 percent of patients who were transitioned to adalimumab (40 mg every other week) following a suboptimal responses to either etanercept, methotrexate or phototherapy achieved PASI 75 at week 16.[83]

Biologics in Children

Etanercept is the only systemic agent that has been evaluated in a randomized, controlled, double-blinded study for the treatment of childhood psoriasis.[84] In this study, 211 children with plaque psoriasis were treated with 0.8 mg/kg (maximum of 50 mg) SC injections weekly. At week 12, 57 percent of patients treated with etanercept reached PASI 75, in contrast to 11 percent in the placebo group. In the open label extension phase, 68 percent of children in the etanercept group and 65 percent of children who originally received placebo achieved PASI 75. Long-term safety of etanercept in children was evaluated in a study of patients with juvenile rheumatoid arthritis who were treated for up to eight years. Over eight years there were no cases of tuberculosis, opportunistic infections, malignancies, lymphomas, lupus or demyelinating disorders or deaths.[85]

CONCLUSION

Biologics have had a profound impact on the treatment of psoriasis and on the quality of life of affected patients. Discussion about systemic treatments for psoriasis including the biologics should occur early in the course of the evaluation and treatment. Systemic therapy for patients with psoriasis should not be limited to patients with widespread disease (or >10% BSA) but also be considered for patients with significant impairment in quality of life. However, systemic treatment including biological, should be used with caution, and they should be offered to patients with appropriate monitoring.

DISCLOSURES

Dr. Kircik is a consultant and investigator, and is on the Advisory Board, for Valeant Pharmaceuticals, Intl., Warner-Chilcott, Intendis, Amgen, Inc., and Galderma Laboratories, LP. He is an investigator, speaker, and is on the Advisory Board for Allergan, Inc. He is a speaker, investigator, consultant, and is on the Advisory Board for OrthoNeutrogena, SkinMedica, Inc., Stiefel Laboratories, Inc., and Connetics Corporation. He is an investigator, consultant and speaker for CollaGenex. He is a consultant and is on the Advisory Board for Colbar. He is a consultant for and stockholder in Johnson & Johnson. He is an investigator and speaker for Leo, PharmaDerm, UCB, and Asteilas Pharma US, Inc. He is an investigator and is on the Advisory Board for Nano Bio and Ferndale Laboratories, Inc. He is a speaker and is on the Advisory Board for Genentech, Inc. He is an investigator for GlaxoSmithKline, PLC, Health Point, LTD, Medicis Pharmaceutical Corp., Navartis AG, Nucryst Pharmaceuticals Corp., Obagi, QLT, Inc., Pfizer, Quatrix, TolerRx, Acambis, Asubio, Berlex Laboratories (Bayer HealthCare Pharmaceuticals), Biolife, Breckinridge Pharma, Centocor, Inc., Combinatrix, Coria, Dow Sciences and Dusa. He is a speaker for Innovail, 3M, Serono (Merck Serono International SA), Triax, Abbott Laboratories, and Dermik Laboratories. He is on the Advisory Board for Biogen-Idec.

Dr. Gonzalez has no relevant conflicts of interest to disclose.

REFERENCES

1. Krueger GG, Feldman SR, Camisa C, et al. Two considerations for patients with psoriasis and their clinicians: What defines mild, moderate, and severe psoriasis? What constitutes a clinically significant improvement when treating psoriasis? *J Am Acad Dermatol*. 2000;43:281-285.
2. Lebwohl M. A clinician's paradigm in the treatment of psoriasis. *J Am Acad Dermatol*. 2005;53(1Suppl 1): S59-S69.
3. Feldman SR, Kimball AB, Kreugar GG, et al. Etanercept improves the health-related quality of life of patients with psoriasis: Results of a phase III randomized clinical trial. *J Am Acad Dermatol*. 2005;53(5):101-107.
4. Finlay AY. Current severe psoriasis and the rule of tens. *Br J Dermatol*. 2005;152(5):861-867.
5. Sterry W, Barker J, Boehncke WH, et al. Biological therapies in the systemic management of psoriasis: International Consensus Conference. *Br J Dermatol*. 2004;151(Suppl 69):3-17.
6. Callen JP, Krueger GG, Lebwohl M, et al. AAD consensus statement on psoriasis therapies. *J Am Acad Dermatol*. 2003;49(5):897-899.
7. Sommer DM, Jenisch S, Suchan M, et al. Increased prevalence of the metabolic syndrome in patients with moderate to severe psoriasis. *Arch Dermatol Res*. 2006;298:321-328.
8. Gelfand JM, Neimann AL, Shin DBet, al. Risk of myocardial infarction in patients with psoriasis. *JAMA*. 2006;296(14):1735-1741.
9. Kimball AB, Guerin A, Latremouille-Viau MA, et al. Coronary heart disease and stroke risk in patients with psoriasis: Retrospective analysis. *Am J Med*. 2010;123(4):350-357.
10. Weiss SC, Kimball AB, Liewehr DJ, et al. Quantifying the harmful effect of psoriasis on health-related quality of life. *J Am Acad Dermatol*. 2002;47(4):512-518.
11. Kimball AB, Geurin A, Yu AP, et al. 2nd World Psoriasis and Psoriatic Arthritis Conference 2009, International Federation of Psoriasis Stockholm, Sweden. June 25, 2009.
12. Rapp SR, Feldman SR, Exum ML, et al. Psoriasis causes as much disability as other major medical diseases. *J Am Acad Dermatol*. 1999;41:201-207.

13. Shiraz G, et al. 6th EADV Spring Symposium, Bucharest, Romania.
14. Seidler EM, Kimball AB et al. *Br J Dermatol*. In press.
15. Seidler EM, et al. 2nd World Psoriasis & Psoriatic arthritis Conference, Stockholm, Sweden. June 25-27, 2009
16. Kreuger G, Koo J, Lebwohl M, et al. The impact of psoriasis on quality of life: Results of a 1998 National Psoriasis Foundation patient-membership survey. *Arch Dermatol*. 2001;137:280-284.
17. Horn EJ, Fox KM, Patel V, et al. Association of patient-reported psoriasis severity with income and employment. *J Am Acad Dermatol*. 2007;57(6):963-971.
18. Prodanovich S, Ma F, Taylor JR, et al. Methotrexate reduces incidence of vascular disease in veterans with psoriasis or rheumatoid arthritis. *J Am Acad Dermatol*. 2005;52:262-267.
19. Burmester GR, Mease P, Dijkmans BA, et al. Adalimumab safety and mortality rates from global clinical trials of six immune-mediated inflammatory diseases. *Ann Rheum Dis*. 2009;68(12):1863-1869.
20. Tyring S, Gottlieb A, Papp K, et al. Etanercept and clinical outcomes, fatigue, and depression in psoriasis: Double-blind placebo-controlled randomised phase III trial. *Lancet*. 2006;7:367.
21. Gelfand JM, Troxel AB, Lewis JD, et al. The risk of mortality in patients with psoriasis: Results from a population-based study. *Arch Dermatol*. 2007;143(12):1493-1499.
22. Revicki DA, Menter A, Feldman S, et al. Adalimumab improves health-related quality of life in patients with moderate to severe plaque psoriasis compared with the United States general population norms: Results from a randomized, controlled Phase III study. *Health Qual Life Outcomes*. 2008;2;6:75
23. Revicki DA, Willian MK, Menter A, et al. Impact of adalimumab treatment on patient-reported outcomes: Results from a phase III clinical trial in patients with moderate to severe plaque psoriasis. *J Dermatolog Treat*. 2007;18(6):341-350.
24. SauratJH, Stringl G, Dubertret L, et al. Efficacy and safety results from the randomized controlled comparative study of adalimumab vs. methotrexate vs. placebo in patients with psoriasis. *Br J Dermatol*. 2008;158:558-566.
25. Gordon KB, Vaishnaw AK, O'Gorman J, et al. Treatment of psoriasis with alefacept: Correlation of clinical improvement with reductions of memory T-cell counts. *Arch Dermatol*. 2003;139(12):1563-1570.
26. Ortonne JP, Lebwohl M, Em Griffiths C, et al. Alefacept-induced decreases in circulating blood lymphocyte counts correlate with clinical response in patients with chronic plaque psoriasis. *Eur J Dermatol*. 2003;13(2):117-123.
27. Krueger GG. Clinical response to alefacept: Results of a phase 3 study of intravenous administration of alefacept in patients with chronic plaque psoriasis. *Eur Acad Dermatol Venereol*. 2003;17 Suppl 2:17-24.
28. Lebwohl M, Christophers E, Langley R, et al. An international, randomized, double-blind, placebo-controlled phase 3 trial of intramuscular alefacept in patients with chronic plaque psoriasis. *Arch Dermatol*. 2003;139(6):719-727.
29. Gordon KB, Langley RG. Remittive effects of intramuscular alefacept in psoriasis. *J Drugs Dermatol*. 2003;2(6):624-628.
30. Goffe B, Papp K, Gratton D, et al. An integrated analysis of thirteen trials summarizing the long-term safety of alefacept in psoriasis patients who have received up to nine courses of therapy. *Clin Ther*. 2005;27(12):1912-1921.
31. Ritchlin CT. The eficacy and safety of alefacept in psoriatic arthritis. *Current Rheumatology Reports*. 2006;8(5):1638-1645.
32. Zaba LC, Suárez-Fariñas M, Fuentes-Ducula J, et al. Effective treatment of psoriasis with etanercept is linked to suppression of IL-17 signaling, not immediate response TNF-α genes *J Allergy Clin Immunol*. 2009;124:1022-1030.
33. Borish LC, Steinke JW. Cytokines and Chemokines. *J Allergy Clin Immunol*. 2003;111(2 suppl):S460-S475.
34. Papp KA, Tyring M, Laha J, et al. A global phase III randomized controlled trial of etanercept in psoriasis: Safety, efficacy, and effect of dose reduction. *Br J Dermatol*. 2005;152:1304-1312.
35. Leonardi CL, Powers JL, Matheson RT, et al. Etanercept as monotherapy in patients with psoriasis. *N Engl J Med*. 2003;349(21):2014-2022.
36. Driessen RJB, Boezeman JB, van de Kerkhof PCM, et al. Three-year registry data on biological treatment for psoriasis: The influence of patient characteristics on treatment outcome. *Br J Dermatol*. 2009;160:670-675.
37. Tyring S, Gordon KB, Poulin Y, et al. Long-term safety and efficacy of 50 mg of etanercept twice weekly in patients with psoriasis. *Arch Dermatol*. 2007;143(6):719-26.
38. Gordon KB, Richard GL, Craig L, et al. Clinical response to adalimumab treatment in patients with moderate to severe psoriasis: Double-blind, randomized controlled trial and open-label extension study. *J Am Acad Dermatol*. 2006;55:598-606.
39. Menter A, Tyring SK, Gordon K, et al. Adalimumab therapy for moderate to severe psoriasis: A randomized, controlled phase III trial. *J Am Acad Dermatol*. 2008;58:106-115.
40. Gordon KB, Langley RG, Leonardi C et al. Clinical response to adalimumab treatment in patients with moderate to severe psoriasis: Double-blind, randomized controlled trial and open-label exension study. *J Am Acad Dermatol* 2006;55(4):598-606.
41. Menter A, Tyring SK, Gordon K et al. Adalimumab therapy for moderate to severe psoriasis: A randomized, controlled, phase III trial. *J Am Acad Dermatol*. 2008;58(1):106-115.
42. Menter A, et al. Summer AAD 2007. Poster 1808.
43. Lecluse LL, Driessen RJ, Spuls PI, et al. Extent and clinical consequences of antibody formation against adalimumab in patients with plaque psoriasis. Arch Dermatol. 2010;146:127-132.
44. West RL, Zelinkova Z, Wolbink GJ, et al. Immunogenicity negatively influences the outcome of adalimumab treatment in Crohn's disease. *Aliment Pharmacol Ther*. 2008;28:1122-1126.
45. Humira package insert.
46. Croom KF, McCormack PL. Adalimumab in plaque psoriasis. *Am J Clin Dermatol*. 2009;10(1):43-50.
47. Gottlieb AB, Evans R, Li Shu et al. Infliximab induction therapy for patients with severe plaque-type psoriasis: A randomized, double-blind, placebo-controlled trial. *J Am Acad Dermatol*.

2004;51:534-542.

48. Reich K, O Nestle F, Papp K et al. Infliximab induction and maintenance therapy for moderate to severe psoriasis: A Phase III, multicentre, double-blind trial. *J Am Acad Dermatol*. 2004;51:534-542.
49. Menter A, Feldman SR, Weinstein GD, et al. A randomized comparison of continuous vs intermittent infliximab maintenance regimens over 1 year in the treatment of moderate-to-severe plaque psoriasis. *J Am Acad Dermatol*. 2007;56(31):e1-e15.
50. Chandran NS, Chong WS. A dramatic response to a single dose of infliximab as rescue therapy in acute generalized pustular psoriasis of von Zumbusch associated with a neutrophilic cholangitis. *Australas J Dermatol*. 2010;51(1):29-31.
51. Maini RN, Breedveld FC, Kalden JR, et al. Therapeutic efficacy of multiple intravenous infusions of antitumor necrosis factor alpha monoclonal antibody combined with low-dose weekly methotrexate in rheumatoid arthritis. *Arthritis Rheum*. 1998;41:1552-1563.
52. Menter A, Reich K, Gottlieb AB, et al. Adverse drug events in infliximab-treated patients compared with the general and psoriasis populations. *J Drugs Dermatol*. 2008; 7(12):1137-1146.
53. Kleyn CE, Griffiths CE. Infliximab for the treatment of psoriasis. *Expert Opin Biol Ther*. 2006;6:797-805.
54. L.L.A. Lecluse, G. Piskin, J.R. Mekkes, et al. Review and expert opinion on prevention and treatment of infliximab-related infusion reactions. *Br J Dermatol*. 2008;159(3):527-536.
55. Cheifetz A, Mayer L. Monoclonal antibodies, immunogenicity, and associated infusion reactions. *Mt Sinai J Med*. 2005; 72:250-256.
56. Wallis RS, Broder MS, Wong JY, et al. Granulomatous infectious diseases associated with tumor necrosis factor antagonists. *Clin Infect Dis*. 2004;38:1261-1265.
57. Kim YJ, Bae SC, Sung YK, et al. Possible reactivation of potential hepatitis B virus occult infection by tumor necrosis factor-alpha blocker in the treatment of rheumatic diseases. *J Rheumatol*. 2010;37(2):346-350.
58. Zein NN. Etanercept as an adjuvant to interferon and ribavarin in treatment-naïve patients with chronic hepatitis C virus infection: A phase 2 randomized, double-blind, placebo-controlled study. *J Hepatol*. 2005;42:315-322.
59. Paradisi A, Caldarola G, Capizzi R, et al. Safety of etanercept in patients with psoriasis and hepatitis C virus assessed by liver histopathology: Preliminary data. *J Am Acad Dermatol*. 2010;62(6):1067-1069.
60. Sicotte NL, Voskuhl RR. Onset of multiple sclerosis associated with anti-TNF-α therapy. *Neurology*. 2001;57:1885-1888.
61. Robinson WH, Genovese MC, Moreland LW. Demyelinating and neurologic events reported in association with tumor necrosis factor alpha antagonism: By what mechanisms could tumor necrosis factor alpha antagonists improve rheumatoid arthritis but exacerbate multiple sclerosis? *Arthritis Rheum*. 2001;44:1977-1983.
62. Brown SL, Green MH, Gershon SK et al. Tumor necrosis factor antagonist therapy and lymphooma development: Twenty-six cases resported to the Food and Drug Administration. *Arthritis Rheum*. 2002;46:3151-3158.
63. Margolis D, Bilker W, Hennessy S, et al. The risk of malignancy associated with psoriasis. *Arch Dermatol*. 2001;137(6):778-783.
64. Okada SK, Siegel JN. Risk of serious infections and malignancies with anti-TNF-α antibody therapy in rheumatoid arthritis. *J Am Med Assoc*. 2006;296(18):2201-2212.
65. Gelfand JM, Dommasch E. Is there truly a risk of lymphoma from biologic therapies? *Dermatol Ther*. 2009;22(5):418-430.
66. Menter A, Gottlieb A, Feldman SR, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis: Section 1. Overview of psoriasis and guidelines of care for the treatment of psoriasis with biologics. *J Am Acad Dermatol*. 2008;58(5):826-850.
67. Vandenbroeck K, Alloza I, Gadina M, et al. Inhibiting cytokines of the interleukin-12 family: Recent advances and novel challenges. *J Pharm Pharmacol*. 2004;56:145-160.
68. Zhu Y, Hu C, Lu M, et al. Population pharmacokinetic modeling of ustekinumab, a human monoclonal antibody targeting IL-12/23p40, in patients with moderate to severe plaque psoriasis. *J Clin Pharmacol*. 2009;49:162-175.
69. Krueger GG, Langley RG, Leonardi C, et al. A human interleukin-12/23 monoclonal antibody for the treatment of psoriasis. *New Engl J Med*. 2007;356(6):580-592.
70. Leonardi CL, Kimball AB, Papp KA et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis:76-week results from a randomized, double-blind, placebo-controlled trial (PHOENIX 1). *Lancet*. 2008;371:1665-1674.
71. Papp KA, Langley RG, Lebwohl M, et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 52-week results from a randomized, double-blind, placebo-controlled trial (PHOENIX 2). *Lancet*. 2008;371;1675-1684.
72. Gordon K, et al. Poster presented at EADV; Berlin, Germany. Poster P1170. October 7-11, 2009.
73. Gordon K, et al. Poster presented at Winter Clinical Dermatology Conference; Kauai, HI. January 2010.
74. Griffiths CE, Strober BE, van de Kerkhof P, et al. Comparison of ustekinumab and etanercept for moderate-to-severe psoriasis. *N Engl J Med*. 2010;362(2):118-128.
75. Lebwohl M, Bagel J, Gelfand JM, et al. From the Medical Board of the National Psoriasis Foundation: Monitoring and vaccinations in patients treated with biologics for psoriasis. *J Am Acad Dermatol*. 2008 58(1):94.
76. Gelfand JM, Gladman DD, Mease PJ, et al. Epidemimology of psoriatic arthritis in the population of the United States. *J Am Acad Dermatol*. 2005;53:573.
77. Brock I, Weldingh K, Lillebaek T, et al. Comparison of tuberculin skin test and new specific blood test in tuberculosis contacts. *Am J Respir Crit Care Med*. 2004;170:65-69.
78. Duchini A, Goss JA, Karpen S, et al. Vaccinations for adult solid-organ transplant recipients: current recommendations and protocols. *Clin Microbiol Rev*. 2003;16:357-64.
79. Gottlieb A, Korman NJ, Gordon KB, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis: Section 2. Psoriatic arthritis: overview and guidelines of care for treat-

ment with an emphasis on the biologics. *J Am Acad Dermatol*. 2008;58(5):851-64.
80. Kircik L, Bagel J, Korman N, et al. Utilization of narrow-band ultraviolet light B therapy and etanercept for the treatment of psoriasis (UNITE): efficacy, safety, and patient-reported outcomes. *J Drugs Dermatol* 2008;7(3):245-53.
81. Gisondi P, Del Giglio M, Cotena C, et al. Combining etanercept and acitretin in the therapy of chronic plaque psoriasis: a 24 week, randomized, controlled, investigator-blinded pilot trial. *Br J Dermatol* 2008;158:1345-1349.
82. Griffiths CEM, Strober BE, Yeilding N, et al. Poster #x 68th Annual AAD Meeting, Miami Beach, FL. March 5-9, 2010.
83. Bissonnette R, Bolduc C, Poulin Y, et al. Efficacy and safety of adalimumab in patients with plaque psoriasis who have shown an unsatisfactory response to etanercept. *J Am Acad Dermatol*. 2010 [Epub ahead of print].
84. Strober BE, et al. *J Am Acad Dermatol*. 2010; in press.
85. Paller A, Siegfried EC, Langley RG, et al. Etanercept treatment for children and adolescents with plaque psoriasis. New Engl J Med. 2008;358:241-251.

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Enhancing the Eyes: Use of Minimally Invasive Techniques for Periorbital Rejuvenation

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ABSTRACT

Facial beauty, specifically of the periorbital complex, is an important component of physical attractiveness and non-verbal communication, and is reflective of chronological age. In fact, eye contact is often the first, and some say the most important, form of interaction between individuals. These properties have made rejuvenation of the periorbital complex highly desirable. In the past, rejuvenating the eye meant the need for invasive surgical treatments. Although these may be necessary in advanced cases, minimally or non-invasive procedures have increasingly become first line treatment options since the advent of topical therapies and minimally invasive procedures, which include botulinum toxin, dermal filler injections, laser and chemical peels, laser skin resurfacing, microdermabrasion and intense pulsed light photorejuvenation. Here, the authors review the anatomy of the periorbital complex, the characteristics of an attractive eye, and a variety of techniques that may be used alone or in combination to achieve "the beautiful eye."

INTRODUCTION

Facial beauty has been a topic of great interest since the beginning of recorded history, and studies of facial attractiveness have been conducted in the fields of art, psychology and, only recently, medicine. Facial beauty is the most important determinant of physical attractiveness, and studies have shown that facial attractiveness is an important factor in social and interpersonal interactions.[1,2] Social and developmental psychologists have shown conclusively that society associates facial beauty with varied positive qualities and characteristics, and individuals with attractive facial features are more likely to experience positive outcomes. It has even been postulated that facial attractiveness serves as an important marker for both overall superior phenotypic and genotypic quality.

One of the most striking elements of facial beauty is the periorbital regions, in this paper, referred to simply as the eyes.[3] In addition to their importance in overall facial appearance, the eyes also reflect an individual's approximate chronological age, and can express a variety of emotions. Many non-verbal communications, including a person's emotions revealed through facial expressions, are largely dependent on the eyes. In fact, eye contact is often the first, and some say the most important, form of interaction between individuals. The periorbital complex serves to transmit a multitude of expressions, thus truly serving as the "window to the soul" and "mirrors of the heart." Very subtle variations in eyebrows, eyelids and pupils can portray a wide spectrum of emotions, which has lead to a sense of intrigue and mystery about the eyes. This quality has made the eyes a topic of folklore and symbol of supernatural power in almost every society from the dawn of civilization.

To achieve the "beautiful eye," the dermatologic surgeon must have a thorough understanding of the anatomy and aesthetics of the periorbital complex, the aging process, the variety of techniques (both surgical and non- or minimally-invasive), and the vast array of products available on the market today. He or she must incorporate the aesthetics of a beautiful eye with an understanding of the four major characteristics of facial attractiveness: averageness, symmetry, sexual dimorphism and youthfulness. The "artist" must use this knowledge base to tailor a unified approach to the individual's unique characteristics, desire, ethnicity and, of course, the current trends in society. Below, the authors will review the anatomy of the periorbital complex, the characteristics of an attractive eye, treatment approaches and, finally, some special considerations.

The Periorbital Region: Anatomy, Aesthetics and the Effects of Aging

The periorbital complex consists of the eyebrows, upper and lower eyelids, glabellar region and pericanthal regions.[4–7] Throughout the periorbital complex, the skin should be smooth, subcutaneous tissue should be appropriately distributed, and the musculoskeletal system should provide adequate support to allow for smooth transitions between the complex concavities and convexities inherent in this region. Each area of the periorbital complex must be analyzed and addressed at time of initial consultation.

The upper eyelid runs from the eyelid margin to the eyebrow superiorly. Aesthetically, the upper eyelid should be full, more so laterally than medially, with a well-demarcated superior palpebral sulcus (upper eyelid skin crease) that is located about 8–11 mm from the superior eyelid margin to divide the eyelid into a lower third and upper two-thirds that laterally flows into

the temporal region smoothly. The visible distance between the upper eyelid margin and the superior palpebral sulcus should be 3–6 mm. The upper eyelid skin crease is located lengthwise between the medial canthus and the lateral orbital rim. Finally, the upper eyelid margin should cover 1–2 mm of the iris. In acquired or congenital blepharoptosis (droopy upper eyelid, commonly termed just ptosis), the upper eyelid margin extends beyond 2 mm leading to constriction of the superior visual field. A common cause is the weakness of the levator palpebrae muscle.

The lower lid extends down from the margin to just below the inferior orbital rim to join the cheek.[4–7] The inferior palpebral sulcus (the inferior eyelid fold), which may or may not be seen, is located 3–5 mm from the lower lid margin. The lower eyelid has a gentle bow from medial to lateral margins, with the lowest point located at the lateral edge of the pupil during head-on gaze, and with the superior margin located just at the bottom of the iris. If there is a drooping of the lower eyelid, part of the white sclera will be visible, termed scleral show. Eyelid skin is the thinnest on the body, at less than 1 mm, with minimal subcutaneous tissue underlying the preseptal and pretarsal skin. There is no fat underlying the pretarsal skin. The transition from this thin eyelid skin to the thicker skin of the eyebrow (located approximately 10 mm below the lower eyebrow hairs) and the cheek skin (below the nasojugal and malar folds) should be gentle and smooth. The subcutaneous tissue consists of loose connective tissue with an absence of fat in the skin overlying the tarsal plate. Changes associated with aging, including fat redistribution, skin laxity and weakness of connective tissue, will make the lower transition more prominent leading to dark circles and puffiness below the eyelids, termed dermatochalasis.

Finally, no talk of beautiful eyes is complete without a discussion of the eyelashes. Eyelashes serve a protective function by acting as a physical barrier and sensor for the blink reflex.[8,9] The upper eyelid has ~100–150 terminal hair follicles arranged in two to three rows.[10] The visible eyelash length tends to be about 7 mm with a growth rate of 0.15 mm/day.[11] Unlike other terminal hair follicles, they are not associated with arrector pili muscle. Additional important characteristics that distinguish eyelashes from scalp hair include a shorter hair cycle duration (~5–12 months) resulting from a much shorter anagen phase, a higher percentage of follicles in the telogen phase (~50%) due to a longer telogen phase, and a lack of sensitivity to androgens. [12] Currently there are no medical means to increase the number of hair follicles, however, changes in the hair cycle due to physiologic changes, pathologic changes or therapeutic interventions, can alter the appearance of eyelashes. In addition to their protective function, the appearance of long, dark, full eyelashes that have a gentle curve away from the globe are considered highly desirable.[13,14] Another important feature of the eye is the palpebral aperture (the visible part of the eyeball), as defined by the area between the commisures and the upper and lower eyelids. There is a great deal of variability, but generally an almond shaped asymmetrical ellipse with a longer medial aspect is thought be the most aesthetically pleasing.

Underlying the periorbital skin is the orbicularis oculi muscle, one of the superficial muscles of facial expression. It covers the tarsus, septum and the bony orbit. The tarsal plate, composed of dense fibrous tissue, is responsible for providing structural support to the lids. The posterior margins of the tarsal plates adjoin the conjunctivae. The orbital septum is a multilayered connective tissue structure that extends from the levator/retractor aponeurosis to the tarsal plate near the lid margins to the periosteal margin of the orbit, holding in place the orbital fat that overlies the globe and intraocular muscles. Like other muscles of facial expression, orbicularis oculi is covered by the superficial musculoaponeurotic system (SMAS), which translates muscle movement into movement of the skin. The palpebral portion of the muscle (overlying the tarsus and septum) is responsible for involuntary blinking while the orbital part is responsible for forced closure. The orbital segment interdigitates with other superficial muscles of facial expression including the frontalis muscle and corrugators supercilii superiorly, the anterior temporalis fascia laterally, and the muscles of the quadratus labii superioris and the zygomaticus complex inferiorly.

The upper eyelid fat pad, divided into the central and medial (nasal) compartments, is located between the septum (anteriorly) and the aponeurotic tissue (posteriorly). The lateral upper lid houses the lacrimal gland. Housing the upper eyelid, preaponeurotic fat is found immediately posterior to the orbital septum and anterior to the levator aponeurosis. A central fat pad and a medial fat pad are described in the upper lid, while the lacrimal gland occupies the lateral compartment. Located superior to this, under the orbital portion of orbicularis oculi, is the retro-orbicularis fat (ROOF), extending to the eyebrow region.

The lower eyelid fat pad is divided into three compartments: the medial (nasal), central and lateral fat pads. Like in the upper eyelid, the fat compartments are demarcated by the retractor aponeurosis posteriorly and the septum anteriorly. Of note, the inferiolateral septum inserts 2 mm inferior to the orbital rim, thus the lateral fat can extend over the orbital rim. Beyond the septum, the orbicularis oculi overlies the sub-orbicularis oculi fat (SOOF). Just inferior the SOOF is the malar fat.

Tear Trough

The tear trough, also known as tear trough deformity, specifically refers to an inferiolaterally-running groove near the inner cantus that begins between the orbicularis oculi muscle and the levator labii superioris muscle at the rim of the medial inferior orbital rim.[15] Superficially, it can be appreciated by the junction of the thin eyelid skin above and the thicker nasal and cheek skin below. This becomes more prominent with aging, although

in some individuals a mild tear trough may be a normal variant even at a young age. In some individuals, the tear trough extends to the lateral aspects, covering the entire infraorbital rim, likely caused by weakening of the orbital septum, leading to an appearance of fullness and prominence of the three lower eyelid fat pads. Furthermore, the SOOF and the malar fat moves inferiorly, leading to prominence of the inferior orbital rim and relative surface depression. In addition, the orbicularis oculi muscle may develop hypertrophy or descent that contributes to an aged appearance of the eye, characterized by tired, sunken eyes with a dark shadow on the lower eyelid. Recent evidence supports volume loss rather than increased fat deposition as the primary contributing factor to the formation of tear trough deformity.[16] However, other contributing factors include skin laxity, volumetric changes, ptosis of the malar region, sun damage, dyschromia, rhytides and prominent vasculature.

The Brow

The eyebrows serve to express emotion and are an important aesthetic element of facial beauty.[4,17–19] Eyebrows are elevated and held in position by the frontalis muscle, while their depression is regulated by the glabellar complex, with contributions by the orbicularis oculi muscle on the lateral aspects. With aging, there can be a loss of the arch, in addition to ptosis of the eyebrow, which can sometimes lead to visual field impairment. Additionally, a relative imbalance between the frontalis muscle and glabellar complex, most commonly due to iatrogenic causes, can change the eyebrow shape and position, sometimes by intent or as an unwanted side effect. There is a fair amount of variability on what constitutes an aesthetically pleasing brow due to variations in overall facial shape, size of the eyes, sex and fashion trend. However, there are a few anatomical landmarks that can aid in defining an "ideal brow" position. The edge of medial eyebrow, the medial cantus and the alar base should lie in the same vertical plane. The edges of medial and lateral eyebrow should lie in the same horizontal plane. The edge of lateral eyebrow, the lateral cantus and the alar base should lie in the same oblique plane. The peak of the eyebrow should be located on the same vertical plane as the lateral limbus. In males, the eyebrow tends to be heavier and less arched when compared to females. In males the eyebrow should lie at the supraorbital rim, while in females it should be located above the supraorbital rim. One common and acceptable variation to the above described "ideal brow" is having the peak of the arch fall just superior to the lateral limbus and having the lateral margin of the brow slightly higher than the medial margin.

The aesthetically pleasing eyebrow's shape length, and position must to be tailored to the shape of the face, size of the eyes and patient's personal preferences. This is reviewed in detail by Alex (2004) and is summarized here.[17] There are five basic eyebrow shapes: curved, sharp angled, soft angled, rounded and flat. Those that are arched can be further defined by the degree of their arch: low, medium and high. Each of these shapes are associated with various emotional and personality characteristics. These characteristics and the overall shape of the individual must be balanced when repositioning the eyebrows. As with other aspects of beauty, symmetry of the eyebrows is an important element. The face and the shape of the eyebrow should be balanced to give an overall pleasing appearance. An excellent example of this concept is the perceived size of the eye based on the location of the eyebrow. If the eyebrow is elevated away from the eye, it leads to the perception of a smaller eye compared to when the eyebrow is closer to the eye. Also, in individuals with deep set eyes, elevation of eyebrow will make the supraorbital rim appear more prominent and exacerbate a hollow appearance. At the same time, too low an eyebrow can lead to limited superior visual field.

The Glabellar Complex

The glabellar complex consists of the corrugator supercilii, the depressor supercilii (sometimes referred to as the medial fibers of the orbicularis oculi) and the procerus muscle. As a group, their activity is responsible for the furrows located at the root of the nose with aging, and perceived expressions of anger, frustration, concern and displeasure. The corruguator muscle runs from its origin at the superior nasal dorsum to the underside of the galea above the eyebrow superficial to the periosteum and deep to the frontalis muscle. It is located about 30 degrees above the horizontal plane and serves as a brow depressor moving the eye downward and medially. The procerus muscle originates at the lower nasal dorsum and travels vertically to insert into the dermis above the eyebrows. Its primary function is to serve as a brow depressor. The depressor supercilii is a thin muscle that runs from its origin at the lateral aspect of the superior nasal dorsum to the underside of the galea. It passes superior to the corrugator muscle and parallel and lateral to the procerus muscle, thus it is also a brow depressor. The muscles of the glabellar complex can be best appreciated when the patient is asked to frown or bring the eyebrows together.

The Lateral and Medial Periocular Region

Radial wrinkles on the lateral aspect of the orbit are commonly called "crow's feet," resulting from repeated contraction of the orbicularis oculi muscle and photoaging. As with all wrinkles, they are dynamic initially, but over time will become static. Occasionally, the zygomatic muscles can also play a role in formation of crow's feet. These are most easily appreciated when a patient is asked to smile.

Regular use of the nasalis muscle can lead to what is termed "bunny lines" on the medial aspect of each eye. Bunny lines are lines located on the sides of the nose, originating near the medial cantus and running medioinferiorly. They can be most easily appreciated by asking a patient to wrinkle (twitch) his or her nose.

The Forehead

Although strictly speaking, the forehead is not part of the periorbital complex; its primary muscle, the frontalis, interacts with procerus, the corrugators of the glabellar complex, and orbicularis oculi to shape the periocular structure, most noticeably the position of the brow. In general, the forehead is twice as long as its height and is free of deep horizontal wrinkles that would give the face an aged appearance.

Reshaping the Periorbital Region

Eyelashes

One cannot escape the number advertisements of cosmeceutical products directed toward enhancing the length, fullness and gentle curvature of the eyelashes. There are a multitude of options available including mascara, eyelash transplants, eyelash extensions and pigment tattooing, but none are a hotter topic than Latisse (bimatoprost).[9]

In 2001, bimatoprost 0.3% ophthalmic solution, a prostaglandin analogue, was approved by the U.S. Food and Drug Administration (FDA) for use in open-angle glaucoma to reduce high intraocular pressure.[20] One of the most common side effects reported in multiple trials was increase in the length, fullness and darkness of eyelashses.[21] This fortunate "side -effect" eventually lead to approval of Latisse for hypotrichosis, and since then its use for cosmetic purposes has exploded.[22,23]

When used for ocular hypertenstion, bimatoprost is thought to act through stimulation of prostaglandin receptors.[24] Prostaglandin receptors, located primarily on the dermal papilla and the outer root sheath, have been shown to regulate hair growth cycle. However, it is currently unclear if bimatoprost's efficacy derives from stimulation of these receptors. Cohen describes unpublished (as of the submission of this article) animal studies showing that a two-week course of bimatoprost alters the hair cycle by specifically decreasing the percentage of follicles in telogen phase with prolongation of the anagen phase, leading to an increase in length.[9] In addition, the mice showed ~20 percent increased thickness in short and medium-sized eyelashes, but not in longer eyelashes, without any increase in the number of hair follicles. Increased pigmentation of eyelashes associated with bimatoprost use has been attributed to an increase in melanin granules through stimulation of tyrosinase, the rate-limiting enzyme in melanin synthesis.[25,26]

A recent 278-patient, multicenter, double-blinded, randomized, placebo controlled study assessed the safety and efficacy in eyelash enhancement of one drop of 0.03% bimatoprost solution applied once daily to the upper eyelid margin using an eye applicator.[9] Efficacy was assessed using digital photography and computer-aided measurements; an investigator rated overall eyelash prominence score termed Global Eyelash Assessment (GEA) on a scale of 1–4 (minimal, moderate, marked and very marked); and a 23-item patient reported outcome questionnaire. The study showed that at week 16, there was a 1.4 mm mean increase in eyelash length, 0.71 mm^2 mean increase in the thickness, and an 18 percent increase in eyelash darkness. By week 8, at least a one grade improvement was noted in 50 percent of subjects, and by weeks 16 and 20 in 78 percent of subjects. The authors also report a statistically significant increase in patient satisfaction with the use of Latisse compared to placebo. The most common side effects of bimatoprost ophthalmic solution in ocular hypertension studies are conjunctival hyperemia, eye dryness and pruritus, periocular hyperpigmentation, and rare but potentially permanent iris pigmentation. With Latisse, the most common side effect is conjuctival hyperemia and a clinically irrelevant change in intraocular pressure.[9] Although further studies will be necessary to fully understand the efficacy, short-term and long-term side effects, and mechanism of Latisse, current evidence suggests that it is safe and effective for enhancing eyelashes, resulting in longer, fuller and darker lashes. More recently, many over-the-counter cosmeceutical products claim to make eyelashes longer, fuller and darker, however their true efficacy is not well-understood.

Skin Rejuvenation

Aging skin is characterized by wrinkles (fine and coarse), roughness, dryness, irregular pigmentation and uneven texture. There are a variety of treatment options including topical therapies, chemical peels, dermabrasion and lasers for the treatment of photodamaged skin.

Topicals

Topical therapies include sunscreens, topical retinoids, alpha hydroxy acid (AHA) based emollients and bleaching agents. The patient must be educated on the harmful effects of UV radiation including photoaging (e.g., wrinkling, dyschromia, etc.) and tumorigenesis.

Protection from UV radiation can include avoidance of sun during peak hours, use of wide brimmed hats and use of broad spectrum sunscreens. In addition to these preventive measures, studies have shown that use of AHAs, such as lactic acid and glycolic acid, can rejuvenate skin via their initial effects at the upper layers of the epidermis by decreasing cell adhesion, thereby improving the process of exfoliation in the stratum corneum leading to thinner basket-weave normalization of the superficial epidermis.[27,28]

Delayed histologic effects of AHAs include thickening of the epidermis, normalization of rete ridges, decreased melanogenesis, and increased synthesis of dermal connective tissue including collagen. The dermal effects likely require higher doses than those found in OTC preparations.

Another commonly used topical therapy with skin-rejuvenating effects is retinoids. Use of topical retinoids on a regular basis

over a period of several months has been shown to improve skin texture, dyschromia and fine wrinkling by promoting keratinocyte differentiation and synthesis of extracellular matrix components, including hyaluronic acid.[29–31] At a histologic level, prolonged use of topical retinoids (four to six months), leads to epidermal hyperplasia, reversal of cellular atypia, a more even distribution of melanin, angiogenesis and increased abundance of dermal supporting elements.[32,33]The major limitation of topical retinoid use is its tendency to cause cutaneous irritation. Today, there are several topical retinoids in various formulations available on the market allowing physicians to match the patient's skin type and sensitivity with the appropriate product.

Finally, many topical products are useful for the treatment of dyschromia, including retinoids, AHAs, hydroquinone and azelaic acid, to name a few. With the growing market of cosmeceuticals, patients have a seemingly endless choice of products that promise anti-aging effects, which may or may not be based on scientifically proven molecules. The physician must be aware of their use, efficacy, side effects and good clinical studies (although only rarely available) in order to provide appropriate guidance.

Dermabrasion

Mechanical and chemical skin resurfacing can be employed for skin rejuvenation. Mechanical skin resurfacing, or dermabrasion, is generally reserved for deep facial scars, but more superficial approaches that improve skin texture and dyschromia have become popular.[34–37] Dermabrasion comprises three subtypes: microdermabrasion, manual dermabrasion and motoroized dermabrasion. The most superficial of the group, microdermabrasion, is carried out using a handheld device that shoots and then recaptures aluminum oxide crystals at a high speed leading to removal of skin up to the superficial spinous layer. Although it is not effective for wrinkles and scars, its advantages include smoothening of the textures, improvement in dyschromia, and little to no downtime. Manual dermabrasion methods involve manual removal of skin using silicon carbide sandpaper, with the depth of skin removal depending on the material, force and duration of the procedure. It is useful in areas that require greater control (both in terms of depth and area) than can be achieved with motorized dermabrasion methods, thus is ideal for periorbital and periocular regions. The increased depth control makes manual dermabrasion effective for deeper scars and wrinkles in addition to its utility for texture and dyschromia issues. Finally, motorized dermabrasion utilizes abrasive material, either wire brush or diamond fraise, driven by a rotary power-driven motor. Motorized dermabrasion removes the epidermis and the upper layer of the dermis, thus can be effective for deep acne, surgical or trauma scars, and epidermal nevi. Because of the bulky instrument and delicate nature of the periorbital skin, motorized dermabrasion is not ideal for periorbital area. In addition, the procedure requires substantial recovery time and has the potential risk of aerosolizing infectious particles.[38]

Peels

Chemical peels, subdivided into superficial, medium and deep depth type, are indicated for use in the treatment of photoaged skin, wrinkles, scarring and dyschromia.[39] Even with the advent of new technologies, chemical peels remain popular because of their long history of safety, efficacy, relatively low cost and relatively minimal downtime. In addition, the choice of agent, concentration and technique employed can be varied to provide more complete control over the pattern of injury induced by chemical peels. Superficial chemical peels are used for acne scarring, mild photoaging, epidermal lesions (lentigines and keratoses), epidermal dyschromia and melasma. One of their major advantages is that they can be used in all skin types with minimal risk of post-inflammatory hyperpigmentation.[40] The limited variety of superficial peels includes 20–40% glycolic acid, 10–20% trichloroacetic acid (TCA) and Jessner's solution (a combination of resorcinol, salicylic acid and lactic acid in 95% ETOH). They induce damage that is limited to the superficial epidermis, thus are generally used for exfoliation only. At higher concentrations, glycolic acid (70%) and TCA (30%) can induce injury to the basal layer, thus leading to regeneration of the entire epidermis. This can be used for acne, mild photoaging and melasma, but are not effective for texture changes, wrinkles,, and dermal remodeling. Superificial chemical peels are generally performed as a series of treatments separated by several weeks. The major side effects associated with superficial chemical peels are local irritation, burning and stinging sensations.

Medium-depth peels are used for mild-to-moderate photoaging, epidermal lesions, dyschromia, mild scarring, mild wrinkling and blending of skin after the use of other resurfacing procedures.[41] Agents used for medium-depth peels include 40–50% TCA, or more commonly today 35% TCA in combination with Jessner's solution, 70% glycolic acid, or solid carbon dioxide. These agents cause injury to the level of superficial reticular dermis. Epidermal necrosis, papillary dermal edema and inflammation induced by medium-depth peels over time lead to increased collagen production, leading to expansion of the dermis. Medium-depth peels are especially useful in patients who have advanced localized photoaging in the periorbial area. After addressing the periorbital area, medium-depth peels can be used in the transitional skin between the periorbital complex and the rest of the face to allow for smooth transition. If periorbital skin itself is being treated with a medium-depth peel, care should be taken to avoid over application (due to thinner skin), exposure into the eye or tears causing the peel to migrate down the cheek leading to linear streaking. Post-procedure, medium-depth peels will lead to edema for one to two days, crust formation during days 4–8 and re-epithelization by one to two weeks.[42]

Deep chemical peels include >50% TCA, phenol or most commonly occluded or unoccluded Baker-Gordon formula (3 mL

of 88% phenol, 2 mL of tap water, eight drops of Septisol and three drops of croton oil).[43] They are primarily indicated for use in treating moderate to severe photoaging, deep wrinkles and extensive actinic keratoses. The injury induced by deep peels reaches to the mid-dermis and thus can be very effective for even deep furrows if done properly. However, its benefits must be balanced with the disadvantages, including risk of scarring, textural changes, pigmentory changes, the potential for cardiotoxicity including arrythmias (requiring pre-op evaluation and continuous cardiac monitoring), significant down time and a regular follow-up for several weeks. If deep chemical peels are performed in the periorbital region, a modified Baker-Gordon formula should be utilized (using mineral oil in place of water and decreasing the drops of croton oil), and extreme caution should be used due to risk of ectropion and scarring. The recovery process and wound healing process is similar to that of the medium-depth peels, except that wound dressings and wound care are necessary to due to more extensive dermal damage, with the end result leading to a more organized and compact dermis and rejuvenated epidermis.

Prior to treatment with chemical or mechanical peels, many physicians will prepare the patient's skin by the use of "bleaching agents" and sun protection to reduce the risk of post-inflammatory hyperpigmenation, and use prophylactic antiviral therapy to minimize the risk of activating herpes.[44] In addition, NSAIDs or even narcotics are used for pain control, and systemic glucocorticoids can be used to minimize inflammatory response, depending on the depth of the peel and the patient.

Photorejuvenation, Lasers and Radiofrequency Devices

Over the last 40 years, lasers have become increasingly more selective and effective in targeting specific components located at various tissue depths. This has lead to expansion of the use of lasers to not only treat cosmetic conditions (including vascular lesions, tattoo removal, hair removal and skin rejuvenation) but also medical conditions (such as warts, keloids and psoriasis). For skin rejuvenation, ablative and non-ablative lasers may be used.[45] In general, ablative lasers achieve greater clinical improvement at the cost of increased morbidity.

Indications for ablative laser resurfacing include photoaging (including rhytides, lentigines, telangiectasisas and actinic keratosis) and scars (for example, those associated with acne, trauma, varicella or surgery). It is especially useful for periorbital and perioral regions because these areas tend to benefit least from surgical facelift procedures. Side effects of ablative laser resurfacing include erythema lasting for several months, post-inflammatory hyperpigmentation, relative hypopigmenation compared to untreated skin, delayed hypopigmenation, aceniform eruptions, irritant contact dermatitis, infection and scarring.[46,48] Thus, the ideal candidate for ablative laser resurfacing is healthy, lightly pigmented and without history of scarring or prior radiation treatment to the area. There is also an increased risk of scarring if the patient has been on isotretinoin for up to two years prior to the resurfacing procedure.[49] A lengthy discussion of the risk and benefits, associated downtime, need for prophylaxis against infections and realistic expectations must be undertaken prior to the procedure.

Ablative laser resurfacing can be carried out using the carbon dioxide and Erbium:YAG laser. Both lead to destruction of the epidermis and part of the dermis, and to remodeling of healthy tissue via wound healing. Full-face resurfacing is generally recommended to avoid demarcation lines, however the periorbital region is an exception to this rule and ablative laser resurfacing can be used on the lower eyelid with low risk of demarcation lines.

Carbon dioxide lasers emit high-energy in short duration using monochromatic 10,600 nm light that preferentially targets water-containing tissue. This leads to vaporization of the tissue, heat-induced collagen contraction, hemostasis via thermal injury and coagulation, and over time to fibroplasia and neocollagen deposition.[50,51] There are several different laser systems on the market, but in general studies have shown them to be comparable when used appropriately.[50,52] Most patients obtain significant improvement of their photoaged skin. Specifically, over 90 percent clinical improvement has been noted in the periorbital region.[53] The major disadvantages of carbon dioxide lasers are prolonged erythema, risk of scarring, hypopigmentation and in rare cases, lower lid ectropion (especially in patients with prior or concurrent eyelid surgery). Carbon dioxide laser treatment is most ideal for patients desiring maximal benefit and who are willing to tolerate prolonged erythema.

The newer IR Erbium:YAG ablative laser emits at 2910 nm wavelength, close to the absorption peak for water, to vaporize the epidermis. Because the depth of tissue penetrance with Erbium:YAG is less than for the carbon dioxide laser, the ablation process can be controlled and titrated more precisely with the Erbium:YAG laser by altering the number of passes and the energy fluence. Clinical studies have shown Erbium:YAG to be effective in treating both superficial and deep wrinkles in the periorbital region.[54]

The major advantages of Erbium:YAG lasers compared to carbon dioxide lasers include minimal thermal damage, decreased intensity and duration of erythema, faster recovery time and a decreased risk of scarring. Some of the main disadvantages of Erbium:YAG lasers compared to carbon dioxide lasers include increased risk of dermal bleeding, lack of immediate collagen contracture, and decreased efficacy on deep wrinkles.

More recently, non-ablative lasers have become the treatment option of choice for many patients who are unwilling to un-

dergo ablative laser resurfacing due to the side-effect profile. Non-ablative lasers used for skin rejuvenation include 585 nm pulsed dye lasers, the 532 nm pulsed KTP laser, the 1450 nm diode lasers, the 1320 nm Nd:YAG lasers, the 1450-nm diode laser, among others. Multiple studies have examined the role of these non-ablative lasers in the treatment of photodamaged skin.[55–59] There is a great deal of variability in the results, but the general trend suggests only moderate efficacy in reduction of mild-to-moderate wrinkles, with little to no benefit for severe wrinkles. Furthermore, the longevity of the benefits is poorly characterized. It is clear from these studies, however, that non-ablative lasers have an excellent safety profile with the most common side effect being transient purpura or pigmentary changes. Despite their minimal efficacy and high variability, the extremely low side-effect profile of non-ablative lasers make them a viable treatment option for young patients with mild photodamaged skin looking for "lunch time" skin rejuvenation.

In the last decade, non-ablative radiofrequency energy has been utilized to target energy to heat the dermis, leading to contracture of the collagen, activation of fibroblasts and generation of new collagen over a period of weeks to months, leading to reduction of wrinkles and appearance of skin tightening.[60,61] In addition, pre-treatment of brow depressors with botulinum toxin can improve the collagen remodeling achieved with radiofrequency devices in the periorbital region.[62] The results achieved with non-ablative radiofrequency devices are modest and are said to last from six months to several years. The best results are achieved when performed in a series of multiple treatments. The major advantage of non-ablative radiofrequency energy is its excellent safety profile.

Photodynamic therapy utilizes a light source, blue light or intense pulsed light (IPL), to activate an exogenous photosensitizer, 5-aminolevulinic acid (ALA) applied to the area of interest.[63,64] Although the exact mechanism of action is unclear, there appears to be activation of an inflammatory response and direct cellular toxicity leading to skin rejuvenation. Several prospective studies have shown improvement in fine lines, shallowness and mottled pigmentation.

Neuromodulation

In addition to skin rejuvenation by topical, chemical, mechanical or laser techniques, almost every aspect of the periorbital complex can be enhanced by use of botulinum toxin. Botulinum toxin is excellent for dynamic wrinkles and can be used as an adjuvant for fillers, non-surgical and surgical facial rejuvenation, especially of the periorbital complex.[62,65–68] Since Carruthers and Carruthers' initial reports in the early 1990s on the use of botulinum toxin to treat wrinkles, it has become the most common cosmetic procedure for facial enhancement.[69] Botulinum toxin is a naturally occurring heterodimeric neuromodulatory polypeptide produced by *Clostridium botulinum*. Its neuromodulatory properties, specifically the ability to weaken, relax or paralyze selected muscles, have been exploited for both cosmetic and medical uses including blepharospasm, hyperhidrosis, achalasia and migraines, to name a few.[70] There are seven different serotypes (A–G) of botulinum toxin based on their specific mechanism of action leading to inhibition of acetylcholine release at the neuromuscular junction. After injection, the heavy chain of the neuropeptide serves to target it to the cholinergic presynaptic membrane leading to internalization via endocytosis.[71] Once the botulinum toxin neuropeptide is internalized, its disulfide linkage breaks, generating free active light chain, which cleaves specific proteins in the secretory pathway (type A targets SNAP-25 while type B cleaves VAMP [vehicle-associated membrane protein]), ultimately leading to blockage of acetylcholine release. Over time, lack of synapse activity leads to degeneration of the neuromuscular junction. Botulinum toxin type A (marketed as Botox® or Dysport®) is most commonly used for cosmetic purposes due to its longer duration of action (three to four months, but sometimes as long as six months) and less discomfort compared to serotype B.[72,73] The effects are irreversible, but efficacy is eventually lost due to generation of new axon terminals.[74] Details about reconstitution, storage and handling can be found elsewhere.[65] In general, 100 U of vacuum-dried botulinum toxin powder is reconstituted using 2.5 mL of 0.9% nonpreserved saline to achieve a final concentration of 40 U/mL. There is much variability in the concentration used in practice because higher concentrations will allow the use of lower volumes, decreasing the diffusion potential and pain associated with injection, while lower concentrations may be desired for large muscles that rely on diffusion (such as the frontalis muscle). Per manufacturing guidelines, once reconstituted, botulinum toxin should be used within four hours; however, a number of studies have shown that its efficacy is retained for several weeks if stored at 4°C.[75] Prior to treatment, appropriate patient selection, education and counseling must take place. Patients should be made aware of the excellent safety profile and efficacy of botulinum toxin, as well as its transient nature, requiring repeated treatments at regular intervals to maintain the desired look. The most common side effects are injection-related local erythema, pain, bruising and headache.[70] A rare but specific side effect of botulinum toxin use in the periorbital region is eyelid ptosis. Botulinum toxin should not be used in patients with active infection or inflammatory skin condition at the site of injection, in patients with a history of neuromuscular disorders (such as myasthenia gravis or Eaton-Lambert syndrome), in patients using aminoglycosides or other drugs that act at the neuromuscular junction or during pregnancy (category C) or lactation.[66]

The Glabellar Complex, Forehead and Brow Shaping

Botulinum toxin can be used to effectively treat rhytides of the glabellar region and forehead, to shape the eyebrows and to diminish upper eyelid heaviness. To treat the glabellar

lines, botulinum toxin is used to weaken the major eyebrow depressors, the corrugator, procerus and depressor supercilii muscles. Identification of the muscles is easily achieved by asking the patient to frown several times. Typically, 20–40 U of botulinum toxin is injected into the glabellar complex using a series of injections. The most commonly used injection sites are the midline and two injections bilaterally just above the medial canthus. If necessary, two more injections can be given just laterally, at approximately the midpupillary line, however these sites have the highest risk of causing ptosis, thus caution must be used. At all times injections should be carried out above the orbital rim to prevent diffusion into the levator muscle. For some individuals, additional injections just above and/or below the midline injection maybe necessary to further weaken the procerus muscle. In general, males tend to require higher doses and more injection points to achieve optimal results. In addition, special consideration must be given when treating Asian eyes because of their unique anatomy. The patient's response to botulinum toxin can be assessed after one to two weeks, if necessary.

Deep horizontal forehead lines develop over time due to activity of frontalis muscle, the primary brow elevators. In individuals with low brows or natural eyebrow ptosis, they may be especially deep due the increased activity of frontalis muscle to maintain the brow in an elevated position. The folds can be accentuated by asking the patient to raise their eyebrows. There is a great deal of variability in treatment of forehead lines, but in general 10–20 U for females (males may require slightly higher doses) are injected into a variable number of sites (four to eight most commonly) on the upper two thirds of the forehead (or 1–2 cm above the brow). Care must be taken not to paralyze the inferior aspect of the frontalis, in order to maintain its function and avoid brow ptosis.

Carefully balanced modulation of brow elevator and depressor muscles using botulinum toxin can allow an advanced practitioner to alter the eyebrow contour. To elevate the medial eyebrow, the medial corrugator injection should be carried out deeply to avoid paralysis of the superficially running frontalis muscles. To raise the lateral eyebrow, a single approach or combination of approaches can be taken. Small amounts of botulinum toxin can be injected into the lateral tail of each eyebrow to weaken the depressor without altering the frontalis muscle. For additional eyebrow elevation, treatment of the crow's feet area should be carried out, as this will further weaken the lateral depressor fibers of eyebrow. For more dramatic flair, one can also inject the medial fibers of the frontalis muscle (central forehead) to drop the medial eyebrow, leading to accentuation of the lateral eyebrow elevation. To raise the eyebrow uniformly, both lateral and medial depressors can be weakened. To achieve an arched brow shape, small amounts of botulinum toxin are injected into the medial and central brow, while leaving the lateral eyebrow untreated. This will result in relative dominance of frontalis on the medial eyebrow leading to its elevation and then gradual tapering down of the untreated lateral eyebrow.

Crow's Feet

Crow's feet can be easily assessed by asking the patient to smile. These radial wrinkles are primarily due to contraction of the orbicularis oculi muscle, but in some patients the zygomatic muscles can contribute to the most inferior wrinkles of the lateral orbit. Crow's feet are effectively treated by injecting a total of 8–12 U of botulinum toxin in a series of three to five injection sites 1–1.5 cm lateral to the orbital rim. After injection, the sites are gently massaged and the patient is asked to squint to allow even diffusion into the area. If the inferior aspects of crow's feet are felt to be due to zygomatic muscles, they should not be corrected because it can lead to asymmetry in the perioral region. Lower lid laxity should be evaluated prior to treatment of the inferior aspects of the crow's feet due to the risk of ectropion and accentuating the drooping of the lower eyelid. As discussed above, treatment of the crow's feet area can lead to mild elevation of the lateral eyebrow. The most common side effect of injecting the crow's feet area is bruising due to abundant superficial vessels in this area.

Bunny Lines

Bunny lines can be effectively treated with low doses (2–5 U) of botulinum toxin, injected superficially into the nasalis muscle. Care must be taken to avoid diffusion into the inferior musculature to avoid lip ptosis.

Hypertrophic Orbicularis Oculi

The pretarsal portion of the orbicularis oculi muscle is in important in regulating the palpebral aperture. Hypertrophy of this muscle can lead to decreased size of the palpebral aperture, and the perception of lower eyelid bags, sometimes referred to as a "jelly roll" appearance to the lower eyelid. This can be treated by injecting 1-2 U of botulinum toxin 3 mm below the lower eyelid margin in the midpupillary line. This technique should be avoided in patients with lower eyelid laxity (which can be tested using the snap test) due to risk of increasing the laxity, leading to scleral show.

Fillers

Soft-tissue fillers are an excellent treatment for correcting the deep folds and static wrinkles that cannot be alleviated by botulinum toxin alone. Fillers also serve to correct volume loss in the periorbital complex that occurs as part of the aging process.[4,15,16,67,76]

The most commonly used fillers in the periorbital region are collagen, hyaluronic acid, autologous fat and poly-L-lactic acid. In general, collagen products are best suited for the superficial fine lines within the periorbital complex including crow's feet, the glabellar complex, horizontal forehead lines (especially those on the lower third of the forehead, where botulinum toxin

is not ideal). Hyaluronic acid, autologous fat, and poly-L-lactic acids are best suited for volume replacement and deeper lines of the forehead and glabellar region.

In the lower eyelid, the primary areas that can be treated with fillers are the orbital rim and the tear trough. The septal confluence, at the junction of the tarsal plate and orbital septum, can also be injected; however, this is quite delicate and should be reserved for the most advanced practitioners.

As noted earlier, pseudoherniation, orbital septal laxity and atrophy of the midface can lead to the appearance of an aged, volume depleted lower eyelid. This can be effectively treated by injecting small aliquots of filler just inferior to the orbital rim at a plane between the periosteum and the orbicularis oculi muscle. The filler material should be carefully massaged to allow for even distribution. Similarly, the tear trough deformity (located inferiormedially to the orbital rim) is filled by using a serial point injection or linear threading technique and massaged using a cotton-tipped swab or a digit. The volume injected varies from patient to patient and overcorrection should be avoided. Better results will be achieved if the patient is reassessed in two to four weeks and then additional treatment is performed to achieve complete correction. Care should be taken to avoid injection through the orbital septum (by staying ~1 cm below the orbital rim), to avoid accentuating pseudoherniation.

Volume augmentation of the upper eyelid has been described using autologous fat transplant in the postseptal area with slightly more volume placed in the lateral portion to provide more fullness. In addition, the brow is filled at a deeper level, leading to elevation of the upper eyelid. There is usually also accompanying volume loss of the temporal area that should be addressed along with the entire face to achieve compete rejuvenation of the periorbital complex.

As with fillers used elsewhere, local anesthesia or topical or local nerve blocks should be used to minimize pain. The most common side effects of fillers include local bruising, erythema, tenderness and edema. Rare but serious side effects include injection site necrosis (most common in the glabellar region), arterial embolization and occlusion of the ophthalmic artery. In addition, depending on the filler agent used, there is a variable risk of hypersensitivity reactions, granuloma reactions, infections and lumps and bumps. Details of these side effects and treatment options are discussed elsewhere.

With proper knowledge of anatomy, products, technique and experience, fillers can be effectively used in the periorbital complex with minimal risk to achieve a beautiful eye.

CONCLUSION

In the past, rejuvenating the eye meant the need for invasive surgical options. Although these may be necessary in advanced cases, invasive surgical procedures have become second-line treatment options since the advent of topical therapies and minimally invasive procedures including botulinum toxin, dermal filler injections, laser, chemical peels, laser skin resurfacing, microdermabration and intense pulsed light photorejuvenation. Studies indicate that patients prefer minimally invasive procedures over traditional surgical options, likely related to their efficacy in achieving good outcomes while minimizing recovery times and having lower side effect profiles.

With the continued seemingly exponential growth and ever increasing experience in minimally invasive procedures to enhance the eyes, a well-versed dermatologic surgeon has an exciting future in enhancing the beauty of eyes.

ACKNOWLEDGEMENTS

The authors thank Robin K. Meray Ph.D., for critical reading and editing of the manuscript.

DISCLOSURES

Dr. Glaser has received research grants from Allergan and Suneva. She is on the advisory board for Medicis, Allergan, and Bioform.

Dr. Patel has no relevant conflicts of interest to disclose.

REFERENCES

1. Langlois JH, Kalakanis L, Rubenstein AJ, et al. Maxims or myths of beauty? A meta-analytic and theoretical review. *Psychol Bull.* 2000;126(3):390-423.
2. Eagly AH, Makhijani MG, Ashmore RD, Longo LC. What is beautiful is good, but…: A meta-analytic review of research on the physical attractiveness stereotype. *Psychol Bull.* 1991;110(1):109-128.
3. McCurdy JA, Jr. Beautiful eyes: Characteristics and application to aesthetic surgery. *Facial Plast Surg.* 2006;22(3):204-214.
4. Volpe CR, Ramirez OM. The beautiful eye. *Facial Plast Surg Clin North Am.* 2005;13(4):493-504.
5. Ross AT, Neal JG. Rejuvenation of the aging eyelid. *Facial Plast Surg.* 2006;22(2):97-104.
6. Rohrich RJ, Coberly DM, Fagien S, Stuzin JM. Current concepts in aesthetic upper blepharoplasty. *Plast Reconstr Surg.* 2004;113(3):32e-42e.
7. Friedman O. Changes associated with the aging face. *Facial Plast Surg Clin North Am.* 2005;13(3):371-380.
8. Randall VA. Hormonal regulation of hair follicles exhibits a biological paradox. *Semin Cell Dev Biol.* 2007;18(2):274-285.
9. Cohen JL. Enhancing the growth of natural eyelashes: The mechanism of bimatoprost-induced eyelash growth. *Dermatol Surg.* 1 Apr 2010. [Epud ahead of print]
10. Khong JJ, Casson RJ, Huilgol SC, Selva D. Madarosis. *Surv Ophthalmol.* 2006;51(6):550-560.
11. Na JI, Kwon OS, Kim BJ, et al. Ethnic characteristics of eyelashes: A comparative analysis in Asian and Caucasian females. *Br J Der-*

matol. 2006;155(6):1170-1176.
12. Randall VA. Androgens and hair growth. *Dermatol Ther.* 2008;21(5):314-328.
13. DeMello M. *Encyclopedia of Body Adornment*. Westport, CN: Greenwood Press; 2007.
14. Hunt N, McHale S. The psychological impact of alopecia. *BMJ.* 2005;331(7522):951-953.
15. Hirmand H. Anatomy and nonsurgical correction of the tear trough deformity. *Plast Reconstr Surg.* 2010;125(2):699-708.
16. Kranendonk S, Obagi S. Autologous fat transfer for periorbital rejuvenation: Indications, technique, and complications. *Dermatol Surg.* 2007;33(5):572-578.
17. Alex JC. Aesthetic considerations in the elevation of the eyebrow. *Facial Plast Surg.* 2004;20(3):193-198.
18. Gunter JP, Antrobus SD. Aesthetic analysis of the eyebrows. *Plast Reconstr Surg.* 1997;99(7):1808-1816.
19. Farkas LG. *Anthropometry of the Head and Face*. 2nd ed. New York: Raven Press; 1994.
20. Woodward DF, Liang Y, Krauss AH. Prostamides (prostaglandin-ethanolamides) and their pharmacology. *Br J Pharmacol.* 2008;153(3):410-419.
21. Patil AJ, Vajaranant TS, Edward DP. Bimatoprost—A review. *Expert Opin Pharmacother.* 2009;10(16):2759-2768.
22. Cohen JL. From serendipity to pilot study and then pivotal trial: Bimatoprost topical for eyelash growth. *Dermatol Surg.* 2010;36(5):650-651
23. Yoelin S, Walt JG, Earl M. Safety, effectiveness, and subjective experience with topical bimatoprost 0.03% for eyelash growth. *Dermatol Surg.* 2010;36(5):638-649.
24. Latisse [package insert]. Irvine CA, Inc.; 2008.
25. Galloway GD, Eke T, Broadway DC. Periocular cutaneous pigmentary changes associated with bimatoprost use. *Arch Ophthalmol.* 2005;123(11):1609-1610.
26. Stjernschantz JW, Albert DM, Hu DN, et al. Mechanism and clinical significance of prostaglandin-induced iris pigmentation. *Surv Ophthalmol.* 2002;47 Suppl 1:S162-S175.
27. Rendon-Pellerano M.I. BEF. The use of glycolic acids in the management of xerosis and photoaging. *J Geriatr Dermatol.* 1996;4 Suppl B:12B-16B.
28. Ditre CM, Griffin TD, Murphy GF, et al. Effects of alpha-hydroxy acids on photoaged skin: A pilot clinical, histologic, and ultrastructural study. *J Am Acad Dermatol.* 1996;34(2 Pt 1):187-195.
29. Kligman AM, Grove GL, Hirose R, Leyden JJ. Topical tretinoin for photoaged skin. *J Am Acad Dermatol.* 1986;15(4 Pt 2):836-859.
30. Kang S, Fisher GJ, Voorhees JJ. Photoaging and topical tretinoin: Therapy, pathogenesis, and prevention. *Arch Dermatol.* 1997;133(10):1280-1284.
31. Weinstein GD, Nigra TP, Pochi PE, et al. Topical tretinoin for treatment of photodamaged skin. A multicenter study. *Arch Dermatol.* 1991;127(5):659-665.
32. Bhawan J, Gonzalez-Serva A, Nehal K, et al. Effects of tretinoin on photodamaged skin. A histologic study. *Arch Dermatol.* 1991;127(5):666-672.
33. Olsen EA, Katz HI, Levine N, et al. Tretinoin emollient cream for photodamaged skin: Results of 48-week, multicenter, double-blind studies. *J Am Acad Dermatol.* 1997;37(2 Pt 1):217-226.
34. Nelson BR, Majmudar G, Griffiths CE, et al. Clinical improvement following dermabrasion of photoaged skin correlates with synthesis of collagen I. *Arch Dermatol.* 1994;130(9):1136-1142.
35. Fulton JE, Jr. Dermabrasion, chemabrasion, and laserabrasion. Historical perspectives, modern dermabrasion techniques, and future trends. *Dermatol Surg.* 1996;22(7):619-628.
36. Orentreich N, Orentreich DS. Dermabrasion. *Dermatol Clin.* 1995;13(2):313-327.
37. Bolognia J, Jorizzo JL, Rapini RP. *Dermatology*. 2nd ed. St. Louis, Mo. ; London: Mosby Elsevier; 2008.
38. Benedetto AV, Griffin TD, Benedetto EA, Humeniuk HM. Dermabrasion: Therapy and prophylaxis of the photoaged face. *J Am Acad Dermatol.* 1992;27(3):439-447.
39. Rubin MG. *Chemical peels*. Philadelphia: Elsevier Saunders; 2006.
40. Bosniak S, Cantisano-Zilkha M, Purewal BK, Zdinak LA. Combination therapies in oculofacial rejuvenation. *Orbit.* 2006;25(4):319-326.
41. Brody HJ. *Chemical Peeling and Resurfacing*. 2nd ed. ed. St. Louis ; London: Mosby; 1997.
42. Brodland DG, Cullimore KC, Roenigk RK, Gibson LE. Depths of chemexfoliation induced by various concentrations and application techniques of trichloroacetic acid in a porcine model. *J Dermatol Surg Oncol.* 1989;15(9):967-971.
43. Manaloto RM, Alster TS. Periorbital rejuvenation: A review of dermatologic treatments. *Dermatol Surg.* 1999;25(1):1-9.
44. Resnik SS, Resnik BI. Complications of chemical peeling. *Dermatol Clin.* 1995;13(2):309-312.
45. Shook BA, Hruza GJ. Periorbital ablative and nonablative resurfacing. *Facial Plast Surg Clin North Am.* 2005;13(4):571-582
46. Nanni CA, Alster TS. Complications of cutaneous laser surgery. A review. *Dermatol Surg.* 1998;24(2):209-219.
47. Bernstein LJ, Kauvar AN, Grossman MC, Geronemus RG. The short- and long-term side effects of carbon dioxide laser resurfacing. *Dermatol Surg.* 1997;23(7):519-525.
48. Sriprachya-Anunt S, Fitzpatrick RE, Goldman MP, Smith SR. Infections complicating pulsed carbon dioxide laser resurfacing for photoaged facial skin. *Dermatol Surg.* 1997;23(7):527-535.
49. Rubenstein R, Roenigk HH, Jr., Stegman SJ, Hanke CW. Atypical keloids after dermabrasion of patients taking isotretinoin. *J Am Acad Dermatol.* 1986;15(2 Pt 1):280-285.
50. Alster TS, Nanni CA, Williams CM. Comparison of four carbon dioxide resurfacing lasers. A clinical and histopathologic evaluation. *Dermatol Surg.* 1999;25(3):153-158.
51. Ross EV, Grossman MC, Duke D, Grevelink JM. Long-term results after CO2 laser skin resurfacing: A comparison of scanned and pulsed systems. *J Am Acad Dermatol.* 1997;37(5 Pt 1):709-718.
52. Kauvar AN, Waldorf HA, Geronemus RG. A histopathological comparison of "char-free" carbon dioxide lasers. *Dermatol Surg.* 1996;22(4):343-348.
53. Alster TS, Garg S. Treatment of facial rhytides with a high-energy

pulsed carbon dioxide laser. *Plast Reconstr Surg.* 1996;98(5):791-794.
54. Caniglia RJ. Erbium:YAG laser skin resurfacing. *Facial Plast Surg Clin North Am.* 2004;12(3):373-377.
55. Zelickson BD, Kilmer SL, Bernstein E, et al. Pulsed dye laser therapy for sun damaged skin. *Lasers Surg Med.* 1999;25(3):229-236.
56. Hohenleutner S, Hohenleutner U, Landthaler M. Nonablative wrinkle reduction: Treatment results with a 585-nm laser. *Arch Dermatol.* 2002;138(10):1380-1381.
57. Goldberg DJ, Whitworth J. Laser skin resurfacing with the Q-switched Nd:YAG laser. *Dermatol Surg.* 1997;23(10):903-906.
58. Dayan SH, Vartanian AJ, Menaker G, et al. Nonablative laser resurfacing using the long-pulse (1064-nm) Nd:YAG laser. *Arch Facial Plast Surg.* 2003;5(4):310-315.
59. Kopera D, Smolle J, Kaddu S, Kerl H. Nonablative laser treatment of wrinkles: Meeting the objective? Assessment by 25 dermatologists. *Br J Dermatol.* 2004;150(5):936-939.
60. Abraham MT, Chiang SK, Keller GS, et al. Clinical evaluation of nonablative radiofrequency facial rejuvenation. *J Cosmet Laser Ther.* 2004;6(3):136-144.
61. Alster TS, Tanzi E. Improvement of neck and cheek laxity with a nonablative radiofrequency device: A lifting experience. *Dermatol Surg.* 2004;30(4 Pt 1):503-507.
62. Glavas IP, Purewal BK. Noninvasive techniques in periorbital rejuvenation. *Facial Plast Surg.* 2007;23(3):162-167.
63. Bitter PH. Noninvasive rejuvenation of photodamaged skin using serial, full-face intense pulsed light treatments. *Dermatol Surg.* 2000;26(9):835-842.
64. Goldberg DJ. Photodynamic therapy in skin rejuvenation. *Clin Dermatol.* 2008;26(6):608-613.
65. Carruthers J, Fagien S, Matarasso SL. Consensus recommendations on the use of botulinum toxin type a in facial aesthetics. *Plast Reconstr Surg.* 2004;114(6 Suppl):1S-22S.
66. Salti G, Ghersetich I. Advanced botulinum toxin techniques against wrinkles in the upper face. *Clin Dermatol.* 2008;26(2):182-191.
67. Maas CS. Botulinum neurotoxins and injectable fillers: Minimally invasive management of the aging upper face. *Otolaryngol Clin North Am.* 2007;40(2):283-290.
68. Frankel AS, Markarian A. Cosmetic treatments and strategies for the upper face. *Facial Plast Surg Clin North Am.* 2007;15(1):31-39.
69. Carruthers JD, Carruthers JA. Treatment of glabellar frown lines with C. botulinum-A exotoxin. *J Dermatol Surg Oncol.* 1992;18(1):17-21.
70. Carruthers J, Carruthers A. Botulinum toxin in facial rejuvenation: An update. *Dermatol Clin.* 2009;27(4):417-425.
71. Brin MF. Botulinum toxin: Chemistry, pharmacology, toxicity, and immunology. *Muscle Nerve Suppl.* 1997;6:S146-168.
72. Spencer JM. Botulinum toxin B: The new option in cosmetic injection. *J Drugs Dermatol.* 2002;1(1):17-22.
73. Flynn TC, Clark RE II. Botulinum toxin type B (MYOBLOC) versus botulinum toxin type A (BOTOX) frontalis study: Rate of onset and radius of diffusion. *Dermatol Surg.* 2003;29(5):519-522.
74. de Paiva A, Meunier FA, Molgo J, et al. Functional repair of motor endplates after botulinum neurotoxin type A poisoning: Biphasic switch of synaptic activity between nerve sprouts and their parent terminals. *Proc Natl Acad Sci U S A.* 1999;96(6):3200-3205.
75. Hexsel DM, De Almeida AT, Rutowitsch M, et al. Multicenter, double-blind study of the efficacy of injections with botulinum toxin type A reconstituted up to six consecutive weeks before application. *Dermatol Surg.* 2003;29(5):523-529.
76. Finn JC, Cox S. Fillers in the periorbital complex. *Facial Plast Surg Clin North Am.* 2007;15(1):123-132.

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Facial Shaping: Beyond Lines and Folds With Fillers

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ABSTRACT

Facial attractiveness is the most important determinant of physical attractiveness, and an important factor in social and interpersonal interactions. The field of facial rejuvenation using minimally invasive procedures has expanded exponentially over the last decade. Historically, aging and the resulting changes were primarily attributed to changes in the skin and the underlying musculoskeletal system. However, more recent understanding of the changes associated with facial aging has shifted the focus to changes in the distribution of subcutaneous fat. With the introduction of seemingly endless varieties of fillers over the last decade, restoration of volume loss by subcutaneous fat, and to some extent bone, has never been easier. Here, the authors review the basic principles that govern facial beauty, facial anatomy, the aging process, and the wide variety of fillers available on the market today that enable a dermatologic surgeon to revitalize the face.

INTRODUCTION

In recent years, there has been a notable increase in the number of aesthetic procedures, with over 10.2 million surgical and non-surgical procedures performed in 2008.[1] According to the American Society for Aesthetic Plastic Surgery (ASAPS), this is greater than five-fold the number of cosmetic procedures performed in 1997. Although the majority of patients are females ages 35–50 years, interest in aesthetic procedures has increased among all age groups and socioeconomic backgrounds. Today, more than 80 percent of these procedures are minimally invasive, including (in descending order of frequency): botulinum toxin, dermal filler injections, chemical peels, laser hair removal and microdermabrasion. Studies indicate that patients prefer minimally invasive procedures over traditional surgical options, likely related to their efficacy in achieving good outcomes while minimizing recovery times and having lower side effect profiles.[2]

Facial Beauty

Facial beauty has been a topic of great interest since the beginning of recorded history, and studies of facial attractiveness have been conducted in the fields of art, psychology and, only recently, medicine.[3] Ancient Greek sculptors developed the Greek canons of proportions based on Egyptian principles. Renaissance artist Leonardo da Vinci emphasized the importance of body and facial proportions in his famous works *Vitruvian Man* and *Male Head in Profile with Proportions*.[4] Although not entirely accurate, these served as blueprints for physical anthropology, mostly focused on facial measurements directly from the skull. [3] More recently, there has been increased attention paid to soft-tissue measurements.[5] In addition, computer programs are now being developed to incorporate the current understanding of facial aesthetics and aid in planning for cosmetic intervention.[6]

Why Beauty?

Over the past 30 years, a multitude of studies of facial attractiveness have been conducted in the field of psychology. Facial attractiveness is the most important determinant of physical attractiveness, and an important factor in social and interpersonal interactions. Social and developmental psychologists have shown conclusively that society associates facial beauty with varied positive qualities and characteristics, and that individuals with attractive facial features are more likely to experience positive outcomes. Indeed, attractive children and adults are often deemed nicer, better, healthier and more intelligent.[7–11] In addition, they are also often treated better, in that more altruistic acts are performed for them, and they are more likely to be believed or to be given the benefit of doubt, even in court of law. Attractive individuals are sometimes perceived to be more qualified for a job, more likely to be promoted, hired, more successful and more compensated.[12–15] Furthermore, attractive individuals are found to be more popular, have greater self-esteem and confidence, be more assertive, have greater dating and sexual experience and enjoy better mental and physical health.[16]

The attractiveness of the human face is a major target of selective mate choice during all stages of courtship, from flirtation through face-to-face copulation.[17] Evolutionary psychologists believe that facial interaction is an important aspect of human interaction because morphologic characteristics such as attractiveness are valid indicators of fitness, health, quality and reproductive value.[18,19] This interpretation is based on Darwin's theories of natural and sexual selection, which state that any characteristic, in this case facial attractiveness, that increases survival or enhances attraction by the opposite sex, will become dominant in the gene pool.[20,21] Thus, facial attractiveness serves as an important marker for both overall phenotypic and genotypic quality.

What is Beauty?

Given the significant impact of facial attractiveness in social interaction, it is important to have an understanding of what constitutes facial beauty. Facial attractiveness is a quality that

is more objective than perceived, and for most parts crosses cultural boundaries.[8,22] The old saying "beauty is in the eye of the beholder" is, in fact, questioned by multiple studies. For instance, studies have shown that humans can distinguish attractive versus less attractive faces from infancy and show signs of preference for the former.[23,24] The components of facial attractiveness are grouped into four major cues: averageness, symmetry, sexual dimorphism and youthfulness/neoteny. The relative contribution of each is still debated.

Averageness can refer to one of two things: an averaged face, i.e., a mathematically generated composite face of multiple individual faces; or an average face, i.e., the prototypical face in a defined population. Averageness is thought to be more attractive, because it represents the genetic heterogeneity in the population and avoids extremes. Per the Darwinian theory, genetic heterogeneity offers a survival advantage in terms of greater immunity from pathogenic organisms.[25] A major argument against this hypothesis is that averageness is perceived as more attractive simply because it exhibits two of the other attributes, symmetry and sexual dimorphism.[26] In addition, in the averaged face, focal variations are minimized, generating softer features that may be viewed as more attractive.

Bilateral symmetry of physical traits, as argued by evolutionary psychologists, reflects an overall high quality of development, which is associated with resistance to pathogens and environmental disturbances, and correlates with genetic heterozygosity.[27] Meta-analyses have shown that in various species, males with decreased asymmetry have a greater mating success.[28] In fact, in humans, males with low asymmetry have increased numbers of sexual partners and infidelities.[29] This has also been shown for females.[30] An alternative explanation offered by some, however, is that the visual system is hard-wired to recognize symmetry, resulting in a preference for facial symmetry.[31]

In addition to a youthful appearance, another component of facial attractiveness is neoteny, or the possession of juvenile features in adulthood. Faces with infant-like features—large eyes, a small nose, round cheeks, smooth skin, glossy hair and lighter coloration—tend to be considered more attractive.[32] Studies have shown that both sexes perceive larger eyes and a small nose to be more attractive than a relatively larger nose and smaller eyes.[33,34]

The presence of sexually dimorphic features also plays a role in facial attractiveness. At birth, males and females differ in small extent, but over time, due to the influence of sex hormones, namely estrogen and testosterone, their facial features become more distinct. Studies have shown that extremes of secondary sexual characteristics are more attractive.[35] Various sexually dimorphic features have been described.[32,36] For example, feminine facial features include a smaller nose, a heart-shaped taper to the lower face, with a smaller lower:upper face ratio, and full vermillion lips. In contrast, smaller eyes, a larger nose, wider jaw and smaller forehead are considered more masculine.[35] However, the role of sexually dimorphic facial features in attractiveness can be complex. In particular, studies have shown that in males, more masculine features were felt by females as less warm, less honest, more dominant and representing lower parental ability, and to a degree were less desired when seeking long-term relationships.[37]

Thus, when planning aesthetic procedures to enhance facial attractiveness, the dermatologist should have a good understanding of the principles that determine facial attractiveness. One must be mindful of symmetry, averageness, sexual dimorphism and youthfulness/neoteny when planning soft-tissue augmentation of cheeks, lips and eyebrows. One must also keep in mind that there are bound to be some mild fluctuations based on the current fashion in that particular society.

Aging Process

The natural aging process affects the skin and underlying facial structures, resulting in gradual, yet dramatic, changes in facial appearance as people age.[38] Over time, the forehead narrows and elongates while the lower face widens and shortens, causing the overall face to transition from the "triangle of youth" to the "pyramid of age." Historically, aging and the resulting changes were primarily attributed to changes in the skin and the underlying musculoskeletal system. However, more recent understanding of the changes associated with facial aging has shifted the focus to changes in the distribution of subcutaneous fat. In order to plan out aesthetic procedures, a basic understanding of the changes associated with aging in skin, subcutaneous fat, muscle and bone is necessary. In addition, it is important to realize that these components are not independent, and thus changing one component, by the process of aging or by cosmetic procedures, can have a profound impact on the face as a whole.

Skin

Starting at age of 20, time causes a linear decrease in the overall thickness of the skin.[39] The largest contributing factor is believed to be ultraviolet (UV) radiation, namely UVA. Actinic damage is clinically seen as pigmentary changes (lentigines, dyschromia), vascular changes (telengiectasia), texture (keratoses), loss of elasticity and rhytides. Histologically, there is a flattening of the rete ridges, loss of dermal-epidermal junction, loss of collagen and disorganization of elastic fibers in the dermal layer of the skin leading to fragile and lax skin.[40,41] Initially, wrinkles are only observed when the face is motion; however, with continual damage to elastic tissue, the dynamic wrinkles become static, present even at rest. Furthermore, the loss of elasticity prevents the skin from accommodating changes in volume due to alterations in subcutaneous fat or the musculoskeletal system.

A wide variety of techniques can be used to counteract mild aging that primarily affects the skin but which only causes minimal changes to the underlying infrastructure of the face. These include the use of sunscreens, retinoids and anti-oxidants, among others, in the form of medical and/or cosmeceutical treatments.[42] Recent studies show that skin texture and tone can be improved by the use of autologous fat and biostimulatory fillers.[43] In addition, dermatologists have the option of utilizing a variety of chemical peels and lasers to rejuvenate the skin.

Subcutaneous Fat

Subcutaneous fat profoundly impacts the complex three-dimensional contours of the face, which consist of a series of smooth transitions between distinct convex and concave entities that are perceived as one.[44–46] During the aging process, redistribution of fat on the face leads to a transition from the youthful heart-shaped or upside down triangle-shaped face to that of the aging pyramid-shaped or pear-shaped face, with increased discernibility of the individual spaces. Initially, the hypertrophy of fat pads, namely the jowls of the lower face and neck, was thought to be the driving force in restructuring the contours of the face. However, over time, volume loss has become accepted as the driving force for the aging process. Starting in the 30s, there is a loss of subcutaneous fat in the periorbital, forehead, glabellar, temporal, malar and buccal cheek areas. At the same time, there is an accumulation of fat in the nasolabial and labiomental folds, jowls, submental areas, premalar areas and chin. These changes collectively lead to the older face having a flattened quality to the cheekbones, a sunken appearance to the lips, and a bulging of the inferior fat pads of the eye, eventually leading to overall loss of fullness and roundness to the face. The recognition of the profound impact of volume loss has lead to a shift in the focus from liposuction of the fat to redistribution of autologous fat or, more recently, the use of a variety of fillers (see below). These techniques have been found to be highly successful in reshaping the natural three-dimensional shape of the face.

Muscles

Although the mechanism and relative significance of muscular and ligamentous changes to aging is debated in the literature, there is no doubt that they play an important role (as seen by the ever-increasing utilization of the muscle paralyzer, botulinum toxin). For a long time, the idea that midface descent was caused by an age-related relaxation of muscles, especially the orbicularis oculi and zygomaticus muscle, led to procedures involving shortening and suspending the musculature to restore the youthfulness of the face.[47] However, in the past decade, the outcomes of facial nerve paralysis, botulinum toxin and radiographic studies have disputed the muscular laxity hypothesis. Facial nerve paralysis leads to softening of the nasolabial, periorbital, glabellar and labiomandibular folds. Utilization of botulinum toxin to weaken or paralyze a wide variety muscles leads to improvement in wrinkles and platysmal bands. Furthermore, a high-resolution MRI study by Gosain et al. demonstrated that there is no change in overall muscle thickness, length, or volume between subjects over age 59 and those aged 16–30.[48] However, more work needs to be done to elucidate the relative contribution of muscular changes to facial aging. In general, it is well accepted that changes in both the musculature and subcutaneous fat are interdependent and changes in one will have an impact on the other. This is further supported by MRI studies by Le Lourn et al., which suggest that the contours of the muscles are dependent on the fat pads located deeper to the musculature, and that, over time, shifts in the fat pads lead to changes in muscle shape and their properties.[49] Furthermore, clinical replacement of volume to the key areas of the face, in place of surgically manipulating the musculature, can yield equally effective if not superior cosmetic results.

Bone

It is critical for cosmetic surgeons to understand the role of underlying structural elements to the overall three-dimensional contour of the face and the subtle changes that take place during the aging process.[50] Studies have shown that changes in the bony structure of the head, face and neck become apparent in the 50s.[51] In females, this is likely due to rapid demineralization of bone after menopause.[52]

Computed tomography has been used to show a variety of changes in the bony structure with aging, including a decrease in the glabellar angle, significant orbital expansion in the supramedial and inferiolateral direction, and volumetric loss of the maxilla and mandible.[53] There is a posterior-inferior rotation of the facial skeleton toward the base of the cranium, with aging. This rotation has been hypothesized to contribute to the undermining of midfacial support, including the inferior orbital rim, contributing to the malpositioning of the lower eyelid, leading to lateral bowing and scleral show. Bony changes in the maxilla lead to sharpening and protrusion of the chin. It is unclear at this time whether preventive care, such as supplementation with vitamin D, calcium or bisphosphonates, has an impact on age-associated changes in facial shape.

Bony changes can be addressed by surgical procedures, or utilizing implants to augment the bony structure of the face. However, as discussed below, fillers can be used effectively to augment mild-to-moderate bony volume loss. Cosmetic surgeons must be able to recognize the potential need for alterations, surgical or non-surgical, to the bony structures that are required for the desired effect, to achieve patient satisfaction.

Fillers for Re-shaping the Face

Based on an understanding of the principles of facial attractiveness and aging, the physician can analyze the complete face to identify the nature of the defects. The next step will be to identify the appropriate treatment option (or combinations thereof), including surgical procedures, minimally invasive surgical options, ablative and non-ablative resurfacing therapies, topical therapies or injectable options including neurotoxins and fillers. In addition, the patient must be educated about the complexity of the defect, the risk and benefits of various treatment options, financial costs, recuperation time and realistic expectations to achieve a successful end result.

As discussed above, volume loss is one of the most important contributors to aging of the face. With the introduction of a seemingly endless variety of fillers over the last decade, restoration of volume by subcutaneous fat and to some extent bone has never been easier. Because of their relatively low side effect profile, smaller financial commitment and minimal recovery time compared to more invasive surgical options, they are now the second most commonly performed cosmetic procedure behind botulinum toxin.[1] It is estimated that the filler market will reach $1 billion this year.[54] For the remainder of this article, the authors will focus on the most common currently available fillers on the market, their uses to reshape the face, their complications and management of those complications.

Dermal fillers vary by composition, duration of action, ease of administration, complications, chemical properties and other factors. Although the search for the perfect dermal filler continues, the large variety of commercially available agents allows the physician to match the properties of a particular filler with the location of defect and the desired effect. It is important to keep in mind that many applications of fillers performed today constitute off-label use. An ideal filler would be expected to have a natural feel relative to native tissue, minimal to no antigenic properties, no hypersensitive reactions, minimal pain, produce consistent and durable results, minimal downtime and minimal inflammation. As currently there is no single filler suitable for all defects, it is important to keep in mind that, often, the best results are achieved by combinations of agents plus other treatment modalities (especially neurotoxins).

Volume replacement strategies have been described as early as the 1890s using fat from the arm to augment facial defects, and the modern era of soft-tissue augmentation began in 1970s with the introduction of bovine-derived collagen.[55] Since then, a number of new biofillers have been introduced to the market, in addition to advancement of autologous fat transfer techniques. Fillers are in general divided into three categories: biodegradable and non-permanent agents (autologous fat, bovine collagen, human collagen and hyaluronic acid); semi-permanent agents (polymethylmethacrylate, calcium hydroxylapatite, porcine collagen and polylactic acid) and permanent agents (silicone).

Bovine and Porcine Collagen

Bovine collagen (Zyderm I®, Zyderm II® and Zyplast®) has been used for over 20 years in over 2 million patients and although its popularity is declining, it remains an acceptable filler.[56] All three forms are derived from an isolated United States (U.S.) cattle herd that is monitored for prions.[57] They are packaged in preloaded syringes in a sterile, phosphate-buffered physiologic saline containing 0.3% lidocaine, 98% type I dermal bovine collagen with the remainder consisting of type III collagen (stored at 4°C). The two Zyderm products vary in concentration of collagen (Zyderm I: 35 mg/mL and Zyderm II: 65 mg/mL). In Zyplast, the collagen is cross-linked with glutaraldehyde, which inhibits collagenase, thereby providing it with increased durability. Generally, a 30-gauge, 0.5-inch needle is used for injection purposes. Zyderm I, which is indicated for use in fine lines and shallow scars, is injected into the papillary dermis by introducing the needle at a ~30° angle to the plane of the skin. Generally, 100 percent overcorrection is necessary as saline will be lost from injected material. Since Zyderm II is more viscous, only 50 percent overcorrection is necessary, and it is injected into the mid dermis, allowing it to be used for moderate fine lines and shallow scars. Zyplast is injected into the deep dermis at a 45–90° angle to correct deep nasolabial folds, marionette grooves and for lip augmentation. No overcorrection is necessary with Zyplast. Over a period of three to six months, injected collagen is degraded by host inflammatory response and collagenases. Because all three bovine-collagen derived products have subtle differences, combination therapy can be used to achieve the desired effect, for example Zyplast can be layered with Zyderm to soften deep nasolabial folds.

Adverse reactions to bovine collagen include non-hypersensitive and hypersensitive reactions.[58–60] The majority of non-hypersensitive reactions are those seen with all fillers, as they are often technique-dependent, including bruising, infection, reactivation of herpes virus and vascular injuries. Of note, visible white areas in the skin have been described in cases in which bovine collagen is injected too superficially. Since most cases of local necrosis reported to date have been with injection in the glabellar region, Zyplast is contraindicated in this area. One of the primary limitations of the bovine-derived collagen is its tendency to cause hypersensitivity reactions in ~5 percent of patients. This can be reduced by performing allergy testing using 0.1 mL of material into the volar aspect of the forearm twice at least two weeks apart. A positive reaction occurring with either test is a contraindication and should preclude further therapy with bovine collagen. In addition, two types of delayed hypersensitivity reactions (seen in 1% of patients even though their two skin tests were negative) are associated with bovine collagen. The first and more common involves the formation

of spontaneously resolving (over one year), non-scarring, indurated granulomas at both the treatment and test sites (usually seen with Zyderm). The second type, more commonly seen with Zyplast (in one to four of 10,000 cases), is the formation of sterile abscesses characterized by painful, tense, erythematous, fluctulant nodules that appear usually days to weeks after injection that require incision and drainage, antibiotics, intralesional steriods for treatment with risk of scarring.

Recently, porcine-derived collagen was introduced to the market and indicated for moderate-to-deep wrinkles and folds.[56] It was cross-linked by sugar moieties to increase its durability to six to 12 months, which allowed it to be classified as semi-permanent. Early studies had shown it to be less immunogenic than its bovine counterpart, possibly more efficacious than bovine collagen and equivalent to competing products.[61,62] However, its opaque nature made it unsuitable for use in the superficial dermis.

Human Collagen

To avoid the risk of hypersensitivity, several human derived collagen fillers have been developed.[63] CosmoDerm 1, CosmoDerm 2 and CosmoPlast are very similar to the bovine-derived counterparts in terms of their consistency, concentration, injection techniques and durability. They are generated from a single isolated human fibroblast-derived cell culture line that is screened for pathogens. Since they have a minimal risk of hypersensitivity reactions, they can be injected at the time of initial consultation. The cosmetic results with human collagen are similar to that of bovine collagen with some evidence for smoother injections. Human-derived collagen is also contraindicated in patients allergic to bovine collagen.

Additional human-derived products that are available but not commonly used include cadaveric collagen, cadeveric fascia and autologous collagen and fibroblasts.[60] Human cadaveric skin is used to harvest intact collagen, elastin fibers and glycosaminoglycans, and packaged into pre-packaged syringes sold as Dermalogen and Cymetra. They are similar to the above-described human collagens in their indication, efficacy and safety profile. Of note, Cymetra has a longer shelf life due to the fact that it comes in a powder form that is reconstituted prior to injection. Human cadeveric fascia fillers, known as Fascian, come in a number of different particle sizes, making it appropriate for large subdermal defects. However, due to its relatively limited use, the need to use large bore needles, and a lack of controlled studies on efficacy and adverse effects, its use is limited in practice. Collagen autografts, marketed as Isolagen (currently available only in U.K.), are obtained from 3-mm punch biopsies used to isolate and culture fibroblasts and collagen, which are then used in a manner similar to other collagen products for soft-tissue augmentation. However, the process and expense associated with Isolagen will likely limit its general use.

Hyaluronic Acid (HA)

The most popular filling agents today are the hyaluronic acid derivatives produced by a number of companies in a wide variety of formulations.[54,60,64,65] The major advantage of HA as compared to collagen-based fillers is the longer duration and better safety profile, while offering similar or slightly better results. HA is a glycosaminoglycan that constitutes an important component of the extracellular matrix. Its physiologic properties and function, namely to serve as a lubricant and withstand compression forces, derives from its highly hydrophilic nature, allowing HA molecules to bind a large quantity of water. Since collagen and elastin fibers are embedded in the HA matrix, it has profound impact on the viscoelastic properties of the skin. Studies have shown that aging leads to a decrease in naturally occurring HA, at least in part leading to the loss of hydration, volume and increased propensity to wrinkle.[66] Furthermore, the simple chemical structure of HA is ubiquitous in nature among species thus minimizing immune mediated adverse reactions. Other useful properties of HA include its propensity to expand and increase volume occupance, as well as isovolumetric degradation, or in other words, the ability to maintain volume as it is degraded, by attracting additional water molecules.[67] The filler maintains 95 percent of its initial volume until the almost complete degradation of HA is achieved. Finally, there is some evidence that injected HA can stimulate de novo production of collagen, inhibit metalloproteinases and upregulate growth factors.[68] Thus, overall, its physiologic properties, durability, lack of hypersensitivity and lack of migration make HA an excellent choice for fillers.

HA products are indicated for use in mid- to deep-dermis for correction of moderate to severe facial wrinkles and folds. In addition, they are used for lip augmentation, tear trough deformities, brow lifting, the infraocular sulcus, periauricular area, earlobe and facial contouring. They have also been used on the dorsum of the hands to rejuvenate the volume loss due to aging. Because of their expansible properties, it is important not to overcorrect the defect. The desired effect lasts approximately six to nine months due to eventual metabolism of HA and elimination by the liver. The amount of HA required to maintain the initial desired effect at subsequent injections is less than the initial injection.

There are number of HA products available worldwide; the four most commonly used products in U.S. will be discussed in detail below. They can be subdivided based on the whether they are animal-derived (Hylaform®, rooster combs) and non-animal derived synthetic HA (NASHA) (Restylene®, Captique™, Juvederm™ and Elevesse™ derived from streptococcus). Each product is available in two to three different formulations (varying worldwide) that differ mainly in the concentration of the filler, with the more concentrated products suitable for deeper injections. Both categories are similar in physical characteristics, in

that they are clear, non-particulate, thick gels that are injected using a 30-gauge needle and molded into the desired shape using manual massage. Because of increased viscosity, HA products in general are more painful at the time of injection than collagen fillers. With the exception of Elevesse, which contains 0.3% lidocaine, all other HA products require the use of topical anesthesia and/or local nerve blocks prior to administration.

A major advantage of HA-based fillers over collagen is the decreased risk of hypersensitivity reactions. As with most fillers, the commonly expected side effects of erythema, bruising, induration, edema and reactivation of herpes are reported in less than 2 percent of patients and are short-lived.[69] Superficial placement of HA can lead to a tindel effect-induced blue lump that can be smoothened by massage, expressed through a simple incision, or degraded by the use of hyaluronidase. As with most fillers, the dreaded complication of vascular occlusion, clinically manifested as immediate blanching and pain, has the potential to cause tissue necrosis. The treatment options include inducing vasodilation with warm compress, massage and topical nitroglycerin. In cases of HA-induced vascular occlusion, the physician has an additional treatment option of hyaluronidase in an attempt to restore the blood flow.[70]

Autologous Fat

Used for over a century, autologous fat is considered one of the safest fillers. It is indicated for nasolabial folds, cheeks, infraorbital area, marionette lines, lips, dorsum of the hands and atrophy secondary to disease states (coup de saber, Parry-Romberg syndrome, and lipodystrophies).[56,60,71–73] Its advantages include lack of immunogenicity, the potential to correct large volume deficits, abundant supply, storage for future use and the possibility of achieving permanent results. The disadvantages include its limitation to correcting only deeper defects, the need for a harvesting procedure and unpredictable viability of the graft, which is largely technique-dependent. Fat is generally harvested from the abdomen, thigh or buttocks under tumescent anesthesia through a small incision. The harvested fat is then injected using a large-bore (16- or 18-gauge) needle. Prior to placement of the fat, aspiration is carried out to avoid placement into vasculature. The filler is than molded into position using firm massage. Any unused harvested fat can be stored for 12–18 months.

Calcium Hydroxylapatite

Radiesse, a semi-permanent calcium hydroxylapatite lasting one to two years, is a filler that is also used for vocal-cord insufficiency, as a radiographic tissue marker and for stress-related bladder sphincter incompetence.[71] It is provided in a 1.0 mL prepackaged syringe as a milky white suspension of 25–45 µm microspheres of calcium hydroxylapatite suspended in an gel composed of glycerin, sodium carboxymethylcellulose and water. Calcium hydroxylapatite is a natural component of bone, thus is non-allergenic, and no allergy testing is required. Its high viscosity requires the use of a slightly larger bore needle (25- to 27-gauge). After local anesthesia (topical or regional), Radiesse is placed in the subdermal plane, or periosteally, and contoured using massage. No overcorrection is required. The product can be palpated for several months, but over time the gel will biodegrade and the calcium hydroxyapatite will serve as a matrix for recruitment of fibroblasts and deposition of collagen.[74] Over a period of months to years, Radiesse will be broken down into calcium and phosphate ions and resorbed, with visibility on radiographs for several years. Calcium hydroxylapatite is used for correction of deep folds, furrows, scars and in the midface to correct for large volume loss. Like all other fillers, side effects of Radiesse include bruising, erythema, edema, reactivation of herpes and vascular compromise. Specifically to calcium hydroxylapatite, lip augmentation should be avoided due to higher risk of mucosal nodule formation.[75]

Poly-L-Lactic Acid (PLLA)

PLLA, now marketed as both Sculptra® and Sculpta Aesthetic®, is a biocompatible, biodegradable synthetic polymer supplied as a lyophilized powder requiring reconstitution with water.[76] Biostimulatory agents such as PLLA, employ the host response in achieving the desired end result. For use as a tissue augmentation device a subclinical inflammatory response followed by encapsulation of the microsphere and subsequent fibroplasia is desired. A few simple, yet critical, technical considerations regarding product preparation (>5 cc H20, >24 hour hydration time) and placement (avoid superficial placement or placement in hyperkinetic muscles around the eye or lip) are important to observe in order to minimize adverse events. Treatment is carried out in multiple sessions where the end point is to "blanket" the surface area to be treated—the more volume needed, the more sessions. Soft tissue augmentation is expected (and FDA-approved) to last greater than 25 months.

Polymethylmethacrylate

Artefill® consists of 30–40 µm inert non-degradable polymethylmethacrylate microspheres suspended in bovine collagen, lidocaine and saline phosphate buffer.[77] It is indicated for use in deep dermal or subdermal locations. Similar to other bovine collagens described above, the injected collagen is degraded by host response in approximately one to three months. Over the same period of time, the microspheres serve as a foundation for the formation of a new collagen matrix, resulting in approximately 50–75 percent of the original augmentation becoming permanent. There is some evidence that smaller injections lead to better encapsulation, thus overcorrection should be avoided and complete correction should be carried out over a series of injections. It is important to advise patients to minimize facial movements for several days after injection to prevent migration. The lev-

el of permanent correction depends on host response, thus the results tend to be better for younger patients. Like other bovine collagen products, allergy testing is required to reduce the risk of an allergic reaction.[57]

Silicone

Silicone is an inert, variably viscous liquid composed of polymerized dimethylsiloxane, and it is the most permanent and among the least antigenic fillers available on the market.[78] There are multiple forms of silicone, however, injectable forms of medical grade silicone used off-label for soft tissue augmentation include Silikon®, Silskin™ and the more viscous AdatoSil™. Generally, silicone is injected using a 30-gauge needle using a microdroplet technique, by serial deposition of very small volumes (0.01 mL) within the deep dermis placed 1–4 mm apart. Because of the permanent nature of silicone, injection technique is very important, and care must be taken to prevent overcorrection. Correction is usually carried out over a series of injections spaced apart by four to six weeks. The injected silicone particles will cause local fibroblast infiltration and become encapsulated by collagen, leading to volume correction. In addition to the common side effects of all fillers, including local erythema, edema and ecchymosis, silicone carries a risk of granuloma, especially if less than medical grade silicone is used. Although the permanence can be an advantage of silicone, it is also one of its major drawbacks, because facial aging is a dynamic process and as such the correction may become less pleasing over time.

DISCUSSION

With the emergence of a wide variety of fillers, almost every aspect of the face (and even non-facial areas such as the dorsum of the hands) can be reshaped, including the forehead, the periorbital complex, malar region, nasolabial folds, perioral region, chin and the jawline.

No single filler is ideal or appropriate for all locations. Thus, the clinician must take care to use his or her knowledge of facial attractiveness, the aging process and the properties of various fillers to choose the appropriate filler, volume, plane of injection and injection technique in order to achieve the desired effect. Often a combination of fillers can be used to offset the advantages and disadvantages of each individual filler.[79]

Fillers are often more effective when combined with other treatment modalities, especially botulinum toxin, because repeated muscle movements can decrease the durability of fillers and increase the risk of migration. Additional treatment modalities including peels, lasers, and in more advanced cases even surgical treatment options, should be explored, employed or referred-out if deemed necessary.

After determining the appropriate treatment, the patient must be educated about realistic expectations, in that no matter which modalities are used to delay or partially restore youthful appearance, no one can escape the aging process. The aging process undoubtedly will cause further alterations in facial appearance over time. As mentioned throughout this article, the physician must be aware of the complications and their treatments (for a detailed discussion, the reader is directed to Hirsch et al.[80] and Sclafani AP et al.[81]).

For a comparison of efficacy of individual filler products, the reader is directed to Carruthers et al.[54] and the primary literature, with the knowledge that rigorous studies in the field of aesthetics are still lacking, as it yet remains a combination of art and medicine. One must also keep in mind that the changes associated with aging are dependent on intrinsic (e.g., genetic makeup, hormones and gender), as well as extrinsic factors (e.g., smoking, UV radiation and nutrition). Patients must be educated to protect themselves from the harmful effects of UV radiation by the regular use of sunscreens. In addition, topical therapies in the form of retinoids or a host of other cosmeceuticals should be utilized to slow the aging process and help maintain augmentations.

The field of facial rejuvenation using minimally invasive procedures has expanded exponentially over the last decade, and the continual development of new technologies will provide the clinician and patients with additional exciting possibilities for face and non-facial rejuvenation.

ACKNOWLEDGEMENTS

The authors thank Robin K. Meray Ph.D., for critical reading and editing of the manuscript.

DISCLOSURES

Dr. Fitzgerald is a trainer and speaker for Allergan, Bioform and Johnson & Johnson; and a trainer speaker and consultant for sanofi-aventis.

Dr. Patel has no relevant conflicts of interest to disclose.

REFERENCES

1. American Society of Plastic Surgeons. Statistics. Available at: http://www.plasticsurgery.org. Accessed 1 May 2010.
2. Small R. Aesthetic procedures in office practice. *Am Fam Physician*. 2009;80(11):1231-1237.
3. Vegter F, Hage JJ. Clinical anthropometry and canons of the face in historical perspective. *Plast Reconstr Surg*. 2000;106(5):1090-1096.
4. Naini FB, Moss JP, Gill DS. The enigma of facial beauty: Esthetics, proportions, deformity, and controversy. *Am J Orthod Dentofacial Orthop*. 2006;130(3):277-282.
5. Borman H, Ozgur F, Gursu G. Evaluation of soft-tissue morphology of the face in 1,050 young adults. *Ann Plast Surg*. 1999;42(3):280-288.
6. Johnston VS, Solomon CJ, Gibson SJ, Pallares-Bejarano A. Human

facial beauty: Current theories and methodologies. *Arch Facial Plast Surg*. 2003;5(5):371-377.
7. Adams GR, Crane P. An assessment of parents' and teachers' expectations of pre school children's social preference for attractive or unattractive children and adults. *Child Dev.* 1978;51.
8. Bernstein IH, Lin TD, McClellan P. Cross- vs. within-racial judgments of attractiveness. *Percept Psychophys*. 1982;32(6):495-503.
9. Dion KK. Children's physical attractiveness and sex as determinants of adult punitiveness. *Dev Psychol*. 1974;10(5):772-778.
10. Eagly AH, Makhijani MG, Ashmore RD, Longo LC. What is beautiful is good, but…: A meta-analytic review of research on the physical attractiveness stereotype. *Psychol Bull*. 1991;110(1):109-128.
11. Etcoff NL. Survival of the Prettiest: The Science of Beauty. New York: Doubleday; 1999.
12. Dipboye RL, Wiback K, Fromkin HL. Relative importance of applicant sex, attractiveness, and scholastic standing in evaluation of job applicant resumes. *J Appl Psychol*. 1975;60(1):39-43.
13. Quereshi MY, Kay JP. Physical attractiveness, age, and sex as determinants of reactions to resumes. *Soc Behav Personal*. 1986;14(1):103-112.
14. Morrow PC, Mcelroy JC, Stamper BG, Wilson MA. The effects of physical attractiveness and other demographic characteristics on promotion decisions. *J Manage*. 1990;16(4):723-736.
15. Frieze IH, Olson JE, Russell J. Attractiveness and income for men and women in management. *J Appl Soc Psychol*. 1991;21(13):1039-1057.
16. Langlois JH, Kalakanis L, Rubenstein AJ, et al. Maxims or myths of beauty? A meta-analytic and theoretical review. *Psychol Bull*. 2000;126(3):390-423.
17. Crawford C, Krebs D. Handbook of Evolutionary Psychology: Ideas, Issues, and Applications. Mahwah, N.J.: Lawrence Erlbaum Associates; 1998.
18. Barber N. The evolutionary psychology of physical attractiveness: Sexual selection and human morphology. *Ethol Sociobiol*. 1995;16(5):395-424.
19. Buss DM. *The Evolution of Desire: Strategies of Human Mating*. New York, NY: BasicBooks; 1994.
20. Darwin C. *On the Origin of Species By Means of Natural Selection: Or, The Preservation of Favoured Races in the Struggle for Life*. London: John Murray, Albemarle Street; 1859.
21. Darwin C. *The Descent of Man, and Selection in Relation to Sex*. London: John Murray, Albemarle Street; 1871.
22. Iwawaki S, Eysenck HJ, Gotz KO. A new visual aesthetic sensitivity test (VAST): II. Cross-cultural comparison between England and Japan. *Percept Mot Skills*. 1979;49(3):859-862.
23. Langlois JH, Roggman LA, Rieserdanner LA. Infants differential social responses to attractive and unattractive faces. *Dev Psychol*. 1990;26(1):153-159.
24. Rubenstein AJ, Kalakanis L, Langlois JH. Infant preferences for attractive faces: A cognitive explanation. *Dev Psychol*. 1999;35(3):848-855.
25. Thornhill R, Gangestad SW. Human facial beauty: Averageness, symmetry, and parasite resistance. *Hum Nature-Int Bios*. 1993;4(3):237-269.
26. Enquist M, Johnstone RA. Generalization and the evolution of symmetry preferences. *P Roy Soc Lond B Bio*. 1997;264(1386):1345-1348.
27. Møller AP, Swaddle JP. *Asymmetry, Developmental Stability, and Evolution*. Oxford, New York: Oxford University Press; 1997.
28. Moller AP, Thornhill R. Bilateral symmetry and sexual selection: A meta-analysis. *Am Nat*. 1998;151(2):174-192.
29. Thornhill R, Gangestad SW. Human fluctuating asymmetry and sexual-behavior. *Psychol Sci*. 1994;5(5):297-302.
30. Fink B, Penton-Voak I. Evolutionary psychology of facial attractiveness. *Curr Dir Psychol Sci*. 2002;11(5):154-158.
31. Gangestad SW, Thornhill R. The evolutionary psychology of extrapair sex: The role of fluctuating asymmetry. *Evol Hum Behav*. 1997;18(2):69-88.
32. Bashour M. History and current concepts in the analysis of facial attractiveness. *Plast Reconstr Surg*. 2006;118(3):741-756.
33. Cunningham MR. Measuring the physical in physical attractiveness: Quasi-experiments on the sociobiology of female facial beauty. J *Pers Soc Psychol*. 1986;50(5):925-935.
34. Cunningham MR, Barbee AP, Pike CL. What do women want: Facial-metric assessment of multiple motives in the perception of male facial physical attractiveness. *J Pers Soc Psychol*. 1990;59(1):61-72.
35. Keating CF. Gender and the physiognomy of dominance and attractiveness. *Soc Psychol Quart*. 1985;48(1):61-70.
36. Komori M, Kawamura S, Ishihara S. Effect of averageness and sexual dimorphism on the judgment of facial attractiveness. *Vision Res*. 2009;49(8):862-869.
37. Perrett DI, Lee KJ, Penton-Voak I, et al. Effects of sexual dimorphism on facial attractiveness. *Nature*. 1998;394(6696):884-887.
38. Friedman O. Changes associated with the aging face. *Facial Plast Surg Clin North Am*. 2005;13(3):371-380.
39. Tan CY, Statham B, Marks R, Payne PA. Skin thickness measurement by pulsed ultrasound: Its reproducibility, validation and variability. *Brit J Dermatol*. 1982;106(6):657-667.
40. Lapiere CM. The aging dermis: The main cause for the appearance of old skin. *Brit J Dermatol*. 1990;122:5-11.
41. Varani J, Dame MK, Rittie L, et al. Decreased collagen production in chronologically aged skin: Roles of age-dependent alteration in fibroblast function and defective mechanical stimulation. *Am J Pathol*. 2006;168(6):1861-1868.
42. Donath AS, Glasgold RA, Glasgold MJ. Volume loss versus gravity: New concepts in facial aging. *Curr Opin Otolaryngol Head Neck Surg*. 2007;15(4):238-243.
43. Vleggaar D, Fitzgerald R. Dermatological implications of skeletal aging: A focus on supraperiosteal volumization for perioral rejuvenation. *J Drugs Dermatol*. 2008;7(3):209-220.
44. Donofrio L, Weinkle S. The third dimension in facial rejuvenation: A review. *J Cosmet Dermatol*. 2006;5(4):277-283.
45. Coleman SR, Grover R. The anatomy of the aging face: Volume loss and changes in 3-dimensional topography. *Aesthet Surg J*. 2006;26(1S):S4-S9.

46. Ascher B, Coleman S, Alster T, et al. Full scope of effect of facial lipoatrophy: A framework of disease understanding. *Dermatologic Surgery*. 2006;32(8):1058-1069.
47. Furnas DW. Festoons, mounds, and bags of the eyelids and cheek. *Clin Plast Surg*. 1993;20(2):367-385.
48. Gosain AK, Klein MH, Sudhakar PV, Prost RW. A volumetric analysis of soft-tissue changes in the aging midface using high-resolution MRI: Implications for facial rejuvenation. *Plast Reconstr Surg*. 2005;115(4):1143-1152.
49. Le Louarn C, Buthiau D, Buis J. The face recurve concept: Medical and surgical applications. *Aesthetic Plast Surg*. 2007;31(3):219-231.
50. Albert AM, Ricanek K Jr., Patterson E. A review of the literature on the aging adult skull and face: Implications for forensic science research and applications. *Forensic Sci Int*. 2007;172(1):1-9.
51. Doual JM, Ferri J, Laude M. The influence of senescence on craniofacial and cervical morphology in humans. *Surg Radiol Anat*. 1997;19(3):175-183.
52. Kloss FR, Gassner R. Bone and aging: Effects on the maxillofacial skeleton. *Exp Gerontol*. 2006;41(2):123-129.
53. Shaw RB Jr., Kahn DM. Aging of the midface bony elements: A three-dimensional computed tomographic study. *Plast Reconstr Surg*. 2007;119(2):675-681.
54. Carruthers J, Cohen SR, Joseph JH, et al. The science and art of dermal fillers for soft-tissue augmentation. *J Drugs Dermatol*. 2009;8(4):335-350.
55. Cooperman LS, Mackinnon V, Bechler G, Pharriss BB. Injectable collagen: A six-year clinical investigation. *Aesthetic Plast Surg*. 1985;9(2):145-151.
56. Ogden S, Griffiths TW. A review of minimally invasive cosmetic procedures. *Br J Dermatol*. 2008;159(5):1036-1050.
57. Murray CA, Zloty D, Warshawski L. The evolution of soft tissue fillers in clinical practice. *Dermatologic Clinics*. 2005;23(2):343-363.
58. Klein AW. Techniques for soft tissue augmentation: An 'A to Z'. *Am J Clin Dermatol*. 2006;7(2):107-120.
59. Owens JM. Soft tissue implants and fillers. *Otolaryng Clin N Am*. 2005;38(2):361-369.
60. Bolognia J, Jorizzo JL, Rapini RP. *Dermatology*. 2nd ed. St. Louis, MO; London: Mosby Elsevier; 2008.
61. Narins RS, Brandt FS, Lorenc ZP, et al. A randomized, multicenter study of the safety and efficacy of Dermicol-P35 and non-animal-stabilized hyaluronic acid gel for the correction of nasolabial folds. *Dermatol Surg*. 2007;33 Suppl 2:S213-221.
62. Monstrey SJ, Pitaru S, Hamdi M, et al. A two-stage phase I trial of Evolence30 collagen for soft-tissue contour correction. *Plast Reconstr Surg*. 2007;120(1):303-311.
63. Bauman L. CosmoDerm/CosmoPlast (human bioengineered collagen) for the aging face. *Facial Plast Surg*. 2004;20(2):125-128.
64. Beasley KL, Weiss MA, Weiss RA. Hyaluronic acid fillers: A comprehensive review. *Facial Plast Surg*. 2009;25(2):86-94.
65. Brandt FS, Cazzaniga A. Hyaluronic acid gel fillers in the management of facial aging. *Clin Interv Aging*. 2008;3(1):153-159.
66. Baumann L. Replacing dermal constituents lost through aging with dermal fillers. *Semin Cutan Med Surg*. 2004;23(3):160-166.
67. Narins RS, Bowman PH. Injectable skin fillers. *Clin Plast Surg*. 2005;32(2):151-162.
68. Wang F, Garza LA, Kang S, et al. In vivo stimulation of de novo collagen production caused by cross-linked hyaluronic acid dermal filler injections in photodamaged human skin. *Arch Dermatol*. 2007;143(2):155-163.
69. Friedman PM, Mafong EA, Kauvar AN, Geronemus RG. Safety data of injectable nonanimal stabilized hyaluronic acid gel for soft tissue augmentation. *Dermatol Surg*. 2002;28(6):491-494.
70. Matarasso SL, Carruthers JD, Jewell ML. Consensus recommendations for soft-tissue augmentation with nonanimal stabilized hyaluronic acid (Restylane). *Plast Reconstr Surg*. 2006;117(3 Suppl):3S-34S.
71. Johl SS, Burgett RA. Dermal filler agents: A practical review. *Curr Opin Ophthalmol*. 2006;17(5):471-479.
72. Bucky LP, Kanchwala SK. The role of autologous fat and alternative fillers in the aging face. *Plast Reconstr Surg*. 2007;120(6 Suppl):89S-97S.
73. Obagi S. Autologous fat augmentation for addressing facial volume loss. *Oral Maxillofac Surg Clin North Am*. 2005;17(1):99-109.
74. Silvers SL, Eviatar JA, Echavez MI, Pappas AL. Prospective, open-label, 18-month trial of calcium hydroxylapatite (Radiesse) for facial soft-tissue augmentation in patients with human immunodeficiency virus-associated lipoatrophy: One-year durability. *Plast Reconstr Surg*. 2006;118(3 Suppl):34S-45S.
75. Jansen DA, Graivier MH. Evaluation of a calcium hydroxylapatite-based implant (Radiesse) for facial soft-tissue augmentation. *Plast Reconstr Surg*. 2006;118(3 Suppl):22S-30S.
76. Vleggaar D. Facial volumetric correction with injectable poly-L-lactic acid. *Dermatol Surg*. 2005;31(11 Pt 2):1511-1517.
77. Cohen SR, Berner CF, Busso M, et al. ArteFill: A long-lasting injectable wrinkle filler material—Summary of the U.S. Food and Drug Administration trials and a progress report on 4- to 5-year outcomes. *Plast Reconstr Surg*. 2006;118(3 Suppl):64S-76S.
78. Duffy DM. Liquid silicone for soft tissue augmentation. *Dermatol Surg*. 2005;31(11 Pt 2):1530-1541.
79. Beer K. Dermal fillers and combinations of fillers for facial rejuvenation. *Dermatol Clin*. 2009;27(4):427-432.
80. Hirsch R, Stier M. Complications and their management in cosmetic dermatology. *Dermatol Clin*. 2009;27(4):507-520.
81. Sclafani AP, Fagien S. Treatment of injectable soft tissue filler complications. *Dermatol Surg*. 2009;35 Suppl 2:1672-1680.

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