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A Review of Biologic Treatments for Psoriasis with Emphasis on Infliximab

S. Pirzada, MD[1]; Z. Tomi, MD, FRCPC[2]; W. Gulliver, MD, FRCPC[2,3]

[1]*Dalhousie University, Halifax, Canada*
[2]*Division of Dermatology, Department of Medicine, Memorial University, St. John's, Canada*
[3]*Newlab Research, St. John's, Canada*

ABSTRACT

Moderate-to-severe psoriasis is known to affect millions of people around the globe. This chronic disease substantially impacts patients by impairing their quality of life, causing psychosocial distress, and creating an ongoing financial burden. The biologics are the newest and most effective therapeutic weapon in the treatment of moderate-to-severe psoriasis and psoriatic arthritis that can significantly alter the course of the disease in a relatively short period of time. There is a need to review the recommended treatment guidelines for moderate- to-severe psoriasis and psoriatic arthritis as the perception and demands of patients are constantly changing. Real world experience with this class of drugs is expanding and more new biologics are becoming available.

Key Words: *Psoriasis, Immunomodulators, Infliximab, Etanercept, Efalizumab, Alefacept, Adalimumab*

Psoriasis is a very common skin disease affecting up to 2.5% of people worldwide including over one million adults in Canada,[1] and more then 250,000 new cases are diagnosed each year. Thirty-five percent of this population has been estimated to have moderate-to-severe disease, affecting between 2%-10% of total body surface area.[2]

According to the Canadian Consensus Statement, moderate-to-severe psoriasis significantly diminishes quality of life regardless of the amount of body surface area involved. A survey conducted by the National Psoriasis Foundation in the U.S. found that the stigma around psoriasis caused many sufferers to avoid social interactions or activities, especially if their lesions may attract undesirable attention or negative comments.[3] Of the patients surveyed, 10% admitted to contemplating suicide as a result of their condition.

The psychosocial impact of psoriasis is increasingly being recognized by treating physicians and further reinforced by patients' experiences. The result is a continuing demand for quick and effective treatment options, no matter how short term the benefits and what the financial implications are on the health care system.

Pathogenesis

Psoriasis has been widely recognized as an immune mediated disease of the skin, where T-cells play a central role in its pathogenesis. Pathophysiology of psoriasis involves an abnormal activation of several types of leukocytes that control cellular immunity and the T-cell-dependent inflammatory process in the skin that accelerates the growth of epidermal and vascular cells in psoriasis lesions.

Psoriatic Arthritis (PsA)

Up to 30% of Canadians with psoriasis develop psoriatic arthritis (PsA).[4] Up to 20% of PsA patients suffer from deforming and destructive effects as the disease advances.[5] PsA can lead to progressive and often irreversible bone and joint damage, making it crucial to diagnose early and initiate treatment to interfere with disease progression. Consequently, early intervention is

important in preventing or slowing the long term effects, since it is estimated that half of those with PsA have already experienced serious joint damage (e.g., bone loss) upon first diagnosis.

Standard Systemic Therapies for Psoriasis

Standard systemic therapies for psoriasis that have been in use by dermatologists for decades include methotrexate, cyclosporine, oral retinoids (acitretin), hydroxyurea (rare), mycophenolate mofetil (rare), PUVA and RE-PUVA. Some standard treatment options (e.g., methotrexate, cyclosporine, acitretin and hydroxyurea) can safely be used in combination with certain of the newer biologic therapies. Given the chronic nature of the disease, it is necessary to give more then one course of any systemic treatment if chosen.

New Systemic Therapies for Psoriasis

A number of systemic biologic therapies have been used for the past several years by dermatologists and rheumatologists, and newer targeted biologic therapies are currently under investigation.

Biologics are immunomodulators and bioengineered proteins (such as antibodies, fusion proteins, or recombinant cytokines) that target the pathological effects of T cells directly. The mechanism of action of these targeted therapies follows one of four strategies:[6,7,8]

- Inhibiting T-cell activation and migration.
- Eliminating activated T cells.
- Inhibiting postsecretory cytokines.
- Inducing immune deviation.

The following biologics have received regulatory approval from the US FDA and Health Canada for the treatment of psoriasis and PsA:

- Infliximab (Remicade®, Schering Canada/ Centocor USA)
- Etanercept (Enbrel®, Amgen/Wyeth)
- Efalizumab (Raptiva®, Serono Canada/Genentech)
- Alefacept (Amevive®, Astellas)
- Adalimumab (Humira®, Abbott)

Infliximab

Infliximab is a chimeric (75% human and 25% murine) monoclonal antibody that specifically targets and binds to TNFα, which has been shown to play a role in rheumatoid arthritis (RA), Crohn's disease (CD), ankylosing spondylitis (AS), psoriasis and psoriatic arthritis (PsA).[2] It is approved by the US FDA for the treatment of active PsA, moderate-to-severe plaque psoriasis, CD, and RA.

Dosage and Monitoring

The preferred RA dose is 5mg/kg IV over 2 hours at week-0, -2, and -6, then 5mg/kg q8 wks. Improvement can be seen after the first few weeks. Screening for latent TB (through a PPD and/or chest x-ray) should be done at baseline. Other optional tests conducted at baseline include: BUN, Creatinine, SGOT, SGPT, Hepatitis C serology, and/or β-HCG. Consider periodic CBC and clinical follow up every 3 months.

Efficacy

In the phase III multi-centre, double blind EXPRESS trial at 32 centres in Europe and Canada, 378 patients were enrolled; trial assessments included skin and nail changes using the Psoriasis Area Severity Index (PASI) and Nail Psoriasis Severity Index (NAPSI). At week-10, 80% of patients treated with infliximab achieved at least a 75% improvement from baseline, and 57% achieved at least a 90% improvement, compared with 3% and 1% in the placebo group ($p<0.0001$). At week-24, PASI 75 (82% for infliximab versus 4% for placebo) and PASI 90 (58% versus 1% for placebo) were maintained ($p<0.0001$). At week 50, 61% achieved PASI 75 and 45% achieved PASI 90 in the infliximab group.[9] The EXPRESS trial also evaluated the impact of long term infliximab maintenance therapy on health related quality of life (HRQoL) in patients with psoriasis.

The IMPACT 2 trial evaluated 200 patients with active PsA who were unresponsive to previous treatments.[10] At week-14, 58% of patients receiving infliximab and 11% of those receiving placebo achieved arthritis response criteria improvement of 20% (ACR 20) and 77% of infliximab patients and 27% of placebo patients achieved no improvements according to the psoriatic arthritis response criteria (PsARC) (both with $p<0.001$). Among the 85% of patients with psoriasis involvement of at least 3% body surface area at baseline, 64% of patients receiving infliximab had at least 75% improvement in PASI compared with 2% of patients receiving placebo at week-14 ($p<0.001$). These therapeutic effects were maintained through week-24. This study also reported that fewer infliximab patients than placebo patients had dactylitis and enthesopathy.

Adverse Effects

Common adverse effects include nausea, abdominal pain, back pain, arthralgia, fatigue, and headache. More serious side-effects include hypersensitivity reactions, infusion reactions, worsening of congestive heart failure (CHF), invasive fungal infections, and a lupus-like syndrome. There is a high risk of infection with pre-existing or recent onset of CNS demyelinating disease, seizure disorders, or those who have received live virus vaccines.[2]

Contraindications

Contraindications include hypersensitivity to infliximab or murine products, CHF (Class III/IV based on guidelines of the New York Heart Association). The pregnancy category is B and lactation safety is not known.[2]

Infliximab can be used in conjunction with methotrexate.

Etanercept

This immunomodulator is a fusion protein of the Fc of human IgG1 and the extracellular TNF receptor. It binds soluble TNF and blocks its interaction with cell surface receptors.[2] It is indicated for moderate-to-severe plaque psoriasis in adults; psoriatic, rheumatoid, and juvenile rheumatoid arthritis; and ankylosing spondylitis.

Dosage and Monitoring

The appropriate dosing for etanercept is 50mg SC b.i.w. for 12 weeks then 50mg SC weekly. The US FDA does not require any monitoring, but it is recommended that the following tests be undertaken at baseline: PPD and/or chest x-ray, BUN, creatinine, SGOT, SGPT, hepatitis C serology, and/or β-HCG. Consider

periodic CBC, ESR and clinical follow up every 3 months.[2]

Efficacy

In clinical studies[2] 47% of patients achieved PASI 75 at 3 months and 54% at 6 months. At 3 months, 71% of patients achieved PASI 50, and 47% achieved a static physician's global assessment (sPGA) rating of "almost clear" or "clear". The median time to PASI 50 and PASI 75 was 1 and 2 months respectively, after start of treatment. Of those patients achieving a PASI 75 at 3 months with 50mg SC b.i.w. for 3 months, 77% maintained their improvement at month-6 with 25mg SC qw.

Adverse Effects

Common side-effects include injection site reactions, cough and respiratory symptoms, infections, headaches, and positive ANA. More serious adverse effects include allergic reactions, leucopenia, pancytopenia, new onset or exacerbation of CNS demyelinating disorders (rare), and an increased incidence of lymphoma (twice the general risk).[2]

Contraindications

Contraindications include hypersensitivity to etanercept or its components, live vaccines, active infections or sepsis, CHF, poorly controlled diabetes, or immunosuppression. Precautions should be taken if concomitant medications include anakinara, natalizumab, TNF-blocking agents, or use in patients with malignancy, renal impairment, asthma, CNS demyelinating disease, or blood dyscrasias. The pregnancy category is B, and lactation safety is not known, however it is secreted in breast milk.[2]

Etanercept can be used in conjunction with methotrexate.

Efalizumab

This biologic is a humanized form of murine antibody directed against CD11a. It inhibits T-cell activation, cutaneous trafficking, and adhesion to keratinocytes through the blockade of LFA-1/ICAM-1 binding. It is indicated for moderate-to-severe plaque psoriasis.

Dosage and Monitoring

Dosing for this immunomodulator should begin at 0.7mg/kg SC for the first week, then hold at 1 mg/kg for the next 11 weeks (to a maximum dosage of 200mg) weekly as maintenance therapy. Improvement can be seen as early as 2 weeks after start of treatment. PASI improvement can be maintained during extended treatment with weekly or every other week dosing. The FDA requires that a platelet count be taken on initiation, then they recommend monthly assessments, that may decrease in frequency with continued treatment (e.g., every 3 months). Other recommended tests conducted at baseline include PPD and/or chest x-ray, β-HCG, liver function tests, respiratory function tests (RFTs), and CBC with differential.[2]

Efficacy

In clinical trials,[2] 22%-39% of patients achieved PASI 75 and 52%-61% achieved PASI 50 at 12 weeks. PASI 50 began 4 weeks after start. At 12 weeks, 19%-32% of patients achieved an sPGA of "almost clear" or "clear". Seventy seven percent of patients achieving PASI 75 maintained their improvement through a second 12-week treatment period.

Adverse Effects

Common side-effects include headache, flu-like symptoms with first dose (i.e., fever, headache, myalgia, and nausea), infection, and elevated alkaline phosphatase. Serious adverse effects include infection, malignancy, thrombocytopenia, and worsening of psoriasis.[2]

Contraindications

Contraindications include hypersensitivity to efalizumab or any murine or humanized monoclonal antibody. Avoid combining with natalizumab. Precautions should be taken if concurrent treatment includes thrombocytopenia, immunosuppression, infection, if the patient is elderly, or has received live vaccines, or if there is a history of malignancy. The pregnancy category is C, and it is unsafe to take during lactation.[2]

A rebound effect is seen with discontinuation in nearly 14% of patients. The median time to relapse is 60-80 days.

Alefacept

Alefacept is a fusion protein of human LFA-3 and the Fc portion of IgG1. It inhibits T-cell activation/proliferation by blocking the LFA-3/CD2 interaction resulting in selective apoptosis of T cells.[2] It is indicated for moderate-to-severe plaque psoriasis.

Dosing and Monitoring

This immunomodulator should be given at a weekly dose of 15mg for 12 weeks, wait 12 weeks, and then consider a second 12-week course. A 16-week cycle is currently under investigation. The maximum reduction in psoriasis is seen at 8 weeks after the last dose. The FDA requires that a CD4 level be taken at baseline and then weekly. Alefacept should be held if the CD4 drops below 250 cells/μL. Other possible tests to undertake include a PPD and /or chest x-ray, β-HCG, CBC with differential, liver function test, and RFTs at baseline.[2]

Efficacy

In clinical trials, 21% of patients achieved PASI 75 and 42% achieved PASI 50 at week-14, with 14% achieving an sPGA of "almost clear" or "clear" (2 weeks post dosing). PASI 50 began 60 days after start. Most patients maintained at least a PASI 50 through the 3 month observation period.[2]

Adverse Effects

Common side-effects include cough, dizziness, nausea, myalgia, chills, pharyngitis, pruritus, injection site reactions, and transaminitis. More serious adverse effects include lymphopenia (10% IM, 22% IV), malignancies, serious infections, hypersensitivity, increased transaminase levels (rare), and cardiovascular events.[2]

Contraindications

Contraindications include a hypersensitivity to alefacept. Use should be discontinued for 1 month if CD4 drops below 250 cells/μL. Precautions should be taken if the patient has an infection, a history of malignancy, or has received live vaccines. The pregnancy category is B and lactation safety is not known.[2]

Adalimumab

This immunomodulator is a recombinant human IgG1 monoclonal antibody against TNFα. It binds to TNF-alpha and blocks its interaction with cell surface TNF receptors.[2] It is indicated for PsA and moderate-to-severe RA.

Dosing and Monitoring

Adalimumab should be given at 40mg SC over 3-5 minutes every 2 weeks for 12 weeks. The frequency can be increased to weekly doses if the patient is not taking methotrexate. The FDA requires that patients be screened for latent TB (PPD and/or chest x-ray), routine CBC/chemistries at baseline, and anti-dsDNA antibodies if lupus-like symptoms are present. In addition β-HCG, liver function tests, and RFT, can be considered at baseline.[2]

Adverse Effects

Common side-effects include injection site reaction, and positive ANA. Serious adverse effects include hypersensitivity reactions, confusion, multiple sclerosis, paresthesia, subdural hematoma, tremor, infection/sepsis, malignancy, and TB.[2]

Efficacy

In a very small trial, two out of two patients achieved PASI 50 by week-12 and week-16 in 2 and by week-20, one out of two patients had achieved PASI 75, which was maintained through week-40.[6]

In another study of 147 patients, 53% pf patients on 40mg adalimumab every other week, 80% of patients taking adalimumab weekly, and 4% of patients taking placebo achieved 75% improvement in PASI score at 12 weeks. Responses were sustained for 60 weeks.[11].

Contraindications

Adalimumab is contraindicated in patients with a hypersensitivity to adalimumab or murine products, chronic or recurrent infections, latent TB, or are immunocompromised.

Avoid concomitant therapy with anakinra and TNF-blocking agents. Precautions should be considered if patients have mild CHF (NYHA Class I/II), or if they require close cardiac monitoring. Discontinue in patients who develop a lupus-like syndrome. Exercise caution when treating elderly patients, or those with pre-existing or recent onset of CNS demyelinating disease. Pregnancy category is B and lactation safety is not known.[2]

Adalimumab can be used in conjunction with methotrexate, steroids, salicylates, and NSAIDs.

Conclusion

From the review of current literature, it is evident that to effectively treat psoriasis new biologics can be considered as one of the more effective and relatively safe options for long-term management. Biologics have not only reduced the time needed to clear the symptoms of this chronic disease, but have also proven to be effective in maintaining a disease-free state for longer durations.

We are seeing a shift from the traditional stepwise approach to more patient-focused treatment strategies for moderate-to-severe psoriasis. Biologics represent the beginning of a new era in the treatment of psoriasis by providing dermatologists with a novel therapeutic approach that can substantially improve the quality of life for their psoriatic patients. As treatment patterns change, accompanied by greater patient awareness and increased demand for biologics, one limitation remains: the cost of biologic therapy is prohibitive. Keeping all the above aspects in view, dermatologists have a responsibility to assess each patient's circumstances based on disease severity, psychosocial state, quality of life issues, as well as financial capacity or health care coverage available in determining which treatment modality is optimal.

References

1. Gupta AK, Langley R, Pouline Y, et al. Pathogenesis of psoriasis and current challenges. *J Cutan Med Surg* (suppl 8):3-7 (2004 Aug).
2. Thomas VD, Yang FC, Kvedar JC. Biologics in psoriasis: a quick reference guide. *J Am Acad Dermatol* 53(2):346-51 (2005 Aug).
3. Guenther L, Langley R, Shear NH, et al. Integrating biologic agents into management of moderate-to-severe psoriasis: a consensus of the Canadian Psoriasis Expert Panel. *J Cutan Med Surg* 8(5):321-37 (2004 Sep-Oct).
4. The Arthritis Society. Psoriatic Arthritis. www.arthritis.ca.
5. The Arthritis Foundation. Psoriatic Arthritis. www.arthritis.org.
6. Lui H, Langley R, Poulin Y, et al. Incorporating biologics into the treatment of psoriasis. *J Cutan Med Surg* (suppl 8):8-13 (2004 Aug).
7. Krueger JG. The immunologic basis for the treatment of psoriasis with new biologic agents. *J Am Acad Dermatol* 46(1):1-23 (2002 Jan).
8. Singri P, West D, Gordon K. Biologic therapy for psoriasis: the new therapeutic frontier. *Arch Dermatol* 138(5):657-63 (2002 May).
9. Reich K, Nestle FO, Papp K, et al. Infliximab induction and maintenance therapy for moderate-to-severe psoriasis: a phase III, multicentre, double-blind trial. *Lancet* 366(9494):1367-74 (2005 Oct).
10. Antoni C, Krueger GG, de Vlam K, et al. Infliximab improves signs and symptoms of psoriatic arthritis: results of the IMPACT 2 trial. *Ann Rheum Dis* 64(8):1150-7 (2005 Aug).
11. 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 extension study. *J Am Acad Dermatol* 55(4):598-606 (2006 Oct).

Rejuvenation of the Lip with Injectables

K.R. Beer, MD
Division of Dermatology, School of Medicine, Duke University, Durham, NC, USA
Department of Dermatology and Cutaneous Surgery, University of Miami School of Medicine, Miami, FL, USA
Palm Beach Esthetic Center, West Palm Beach, FL, USA

ABSTRACT

As the range of soft tissue augmentation products proliferates, most will be used (with varying degrees of success) to shape and augment the lip. The range of outcomes for this indication depends on the skill of the injector, the anatomy of the patient and the intrinsic properties of the product. Permutations of these interacting factors are infinite and it is the range of combinations that is responsible for the complexity (and fascination) of lip rejuvenation with injectable products. Based on personal experience, the perfect lip is the one that "wows" the patient and makes them happy with the procedure. Individualizing the injection is of paramount importance and should take priority over a formulaic approach that defines each lip injection as identical. This review will discuss some of the factors that should be considered prior to injecting a lip with soft tissue augmentation products.

Key Words: *Lip rejuvenation, Injectables*

Pre-treatment Consultation

The most important aspects of the lip rejuvenation procedure are an understanding of the patient's goals and an appreciation of her anatomy as it relates to these goals. Prior to any decision regarding which filler may be appropriate, it is worth discussing what the goals are. Providing a mirror and allowing the patient to talk about what she would like to see when she looks in the mirror will facilitate a better understanding of what will be perceived as a successful procedure for that individual. As with any cosmetic procedure, it is important to document the pre-treatment state with photographs and to capture any limitations (such as a constraint on the amount of material used) imposed during the consultation. Initial discussions must also include the range of products available for lip augmentation and the relative risks and benefits of the ones suitable for a particular patient.

Clinical Evaluation

When assessing the lips, I divide patients into three basic categories:

Group 1 - those that have good shape and definition but who desire augmentation of certain features of their lips

Group 2 - those that have atrophic lips requiring augmentation

Group 3 - those that have loss of lip definition and/ or perioral rhytids.

Although each of these categories has a fundamentally different approach, it is not possible to entirely isolate patients into any one category. Consequently, use of these concepts is intended only as a guideline in formulating an approach to treatment. There are other approaches to injecting the lips[1,2] and the reader is encouraged to review several articles in order to decide what aspects of each to integrate.

Injections into the lip are painful and prior to injecting the lips with any product, most patients will benefit from anesthesia. The use of dental topical anesthetic and gingival "miniblocks" (small injections of anesthesia made into the gingival sulcus)[3] will enable the physician to inject without having to rush and provide a more positive patient experience. One other technique that is helpful for obtaining anesthesia of the lip is to utilize a device known as "The Wand™" (Compudent, Inc.) that delivers a gradual, measured dose of anesthetic. For patients who prefer not to have injectable anesthesia, topical alternatives may be helpful.

Group 1

Patients with good lip shape (Figure 1a) that want lip enhancement through augmentation (Figure 1b) are technically the most challenging because they already exhibit a nice appearance prior to treatment. These patients tend to be women between 20-45 years of age with a clear idea of their desired outcome; some will bring pictures of what they want to the consultation. For these women, the first consideration from a physical perspective is the choice of filler. Hyaluronic acid fillers are the most versatile products for this indication, e.g., Restylane® (Q-Med), Perlane® (Q-Med), and Juvederm™ (Inamed), although collagen-based fillers such as Evolence™ (ColBar LifeScience), CosmoPlast® (Inamed) and CosmoDerm® (Inamed) may also be utilized. The dermal filler that is selected depends on the patient's financial constraints, the experience of the injector, and the desired duration of the correction. In general, Perlane® and Restylane® are thicker materials that can add significant volume and structure while Juvederm™ is smoother and less viscous, thus having the ability to flow more consistently. It is important to understand and experience how each product interacts with the lips during injections for different indications and to develop a palette of products depending on the outcome sought.

In order to provide an esthetically pleasing lip augmentation, many physicians begin by injecting into the "wet-dry" junction (the border of the mucous membrane and epithelial layers). This is easily identified in most people as the area where the Fordyce glands end. Eversion of the lip, followed by gentle, gradual injections into this area will inflate the lip. A serial puncture and linear threading technique may be used. Depending on the person's anatomy and the material, one may notice that filler extravasates into small blebs during the injection process. If this occurs, massage or guidance by

the nondominant hand can usually move the product into the correct location. Once the desired augmentation has been approximately achieved, it is important to ensure that the configuration is also as intended. By orienting the needle in a superior manner, injections of small amounts of material into the Cupid's bow of the lip will help to provide perfect definition of this essential aspect. As with injections of the marionette lines, it is helpful to inject the lateral aspects of the lower lip and to ensure their orientation in a horizontal manner. For the upper lip, small amounts of material are injected laterally to avoid a lip that fades away on the sides.

Once the lips are approximately the correct size and shape, small injections are utilized to finesse the outcome. In general, injections into the rolled border of the lips will provide an added dimension of definition. These adjustments are performed by inserting the needle into the rolled border and gently injecting material. For patients who have not had injections before, there is usually a potential space that can be cannulated. Frequently, a very small amount of pressure can be used to inject material that will flow across the lip for distances of up to half of the mouth. This type of injection will serve to highlight the lip as a distinct anatomic region and tends to produce a highly desired esthetic result.

Group 2

The second category of patients, those with atrophic lips (Figure 2), may have small lips due to aging or genetics. These individuals tend to need some additional counseling during the initial consultation so that they understand the limitations of the proposed procedure. Material selection for these patients requires a similar analysis as the former category of patients (Group 1). In general, the hyalurons or collagen-based fillers are the most suitable choices. Injections for treatment of lip atrophy begin with injections into the wet-dry junction, adding the desired amount of volume to both the upper and lower lips. Additional injections are then made into the Cupid's bow and the two medial protuberances of the lower lip, which will provide visual focal points for observers and photography.

In general, atrophic lips tend not to have the anatomic distinctions and inflection points seen in patients presenting for augmentation of normal sized lips. This means that injections into the body of the lip, which provide volume and structure to a previously anatomically bland feature of the face, will inevitably be perceived as an improvement. To maximize the extent of this improvement, it is important to observe each patient and to highlight certain aspects. Injections to evert the lips can produce an appearance of fuller lips, and these may be achieved by injecting the lips as they are rolled outwards and by placing the needle at the wet-dry junction oriented towards the rolled borders.

Group 3

Lip rejuvenation primarily for the treatment of perioral rhytids (Figure 3) is a procedure commonly requested by patients who are typically older than 50 years of age, and who smoke, or are former smokers. This treatment requires more attention to material selection than other procedures. For patients with thin skin and etched-in perioral rhytids, the use of a thin product, such as Restylane® Fine Lines, Evolence® Breeze, Cosmoderm® II, or Juvederm™ 24 is appropriate.

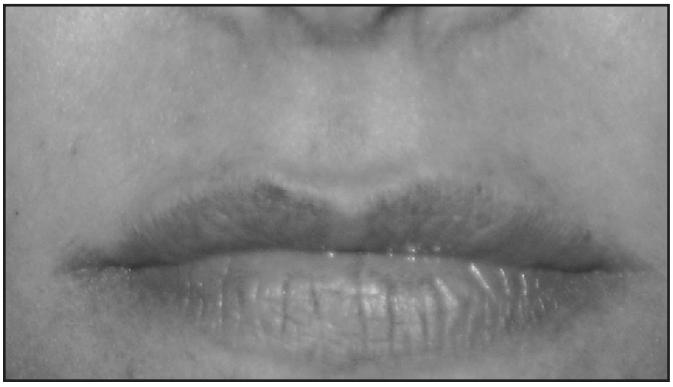

Figure 1a: A patient with good lip shape, pretreatment

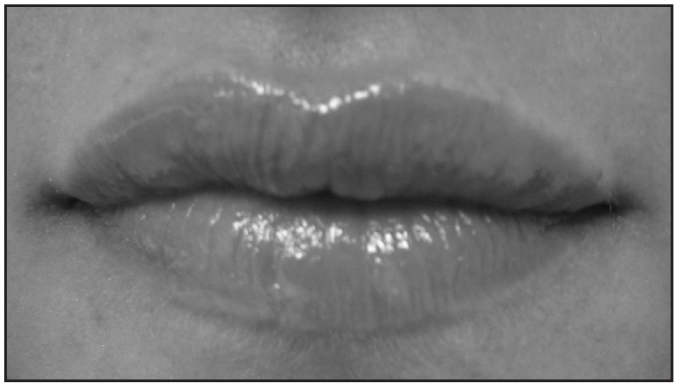

Figure 1b: A patient with good lip shape, posttreatment

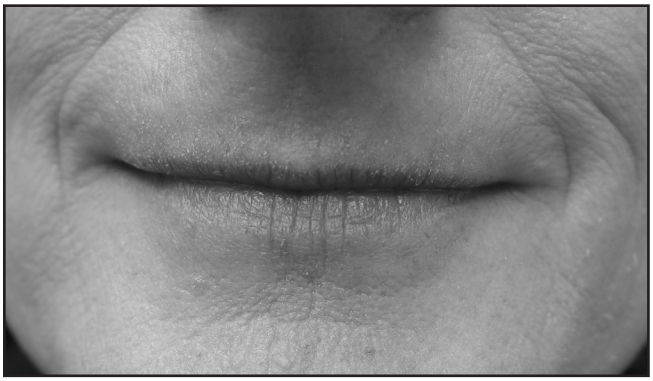

Figure 2: A patient with atrophic lips

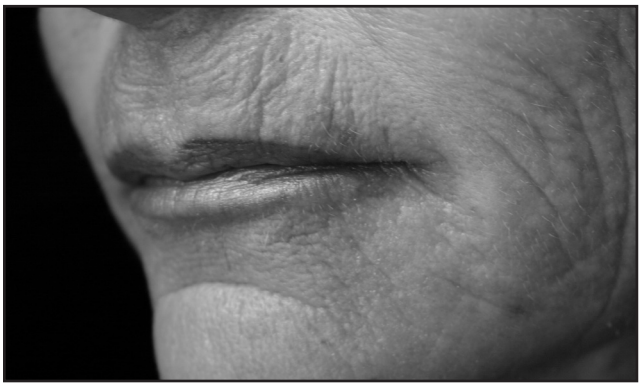

Figure 3: A patient with perioral rhytids

Whereas other injections of the lip may be accomplished with 30G needles, perioral rhytid rejuvenation may be best accomplished with a 32G needle in some patients. In addition to the use of fillers for rejuvenation, this indication frequently requires adjunctive treatments. These may include traditional resurfacing with a CO_2 laser, fractional resurfacing, or the use of botulinum toxins (BOTOX®, Allergan). Used judiciously, this latter addition may produce the most synergistic results in this area. When injecting botulinum toxins, it is helpful to begin by injecting small amounts of material injected into the orbicularis oris in strategic locations, each of which is identified by the prominence of the dynamic component of the perioral rhtyids. When using BOTOX®, approximately 2 units are injected into each of four locations.[4] Other toxins may also be utilized for this indication.

Two types of injections are useful when treating perioral rhytids: those that fill the lines and those that define the lip. In order to fill each line, the needle should be inserted at the junction of the rhytid and the lip, oriented along the course of the rhytid. Using the thumb and second finger of the non-dominant hand to guide the product into place, gentle pressure should be used to inject the product. Following the injection, firm pressure should be applied to smooth out the filler and ensure that it fills but does not overcorrect the rhytid. One common mistake that occurs when injecting perioral rhytids for lip rejuvenation is to overcorrect thereby trading a series of bumps for the rhytids.

Once the individual rhytids are filled, attention should shift to the rolled border of the lips. Since the chief complaint of most female patients with perioral rhytids is lipstick "bleeding" into the lines around their mouth, providing a border for the vermillion will help to confine lipstick to the vermillion and limit its extension into the adjacent areas. To provide this junction, the needle should be inserted into the rolled border and a small amount of material injected. Careful observation of the injection site is essential in order to prevent lip augmentation when definition is the goal. In most patients with perioral rhytids, there is a degeneration of the collagen and elastic fibers around the mouth that facilitates the injection into the border and a small amount of material can flow a long distance from the point of insertion.

Conclusion

Injecting the lips with soft tissue augmentation products can be technically challenging, but can also be extremely rewarding for both the patient and physician. A thorough understanding of the anatomy of the areas involved, as well as of the physical properties of the products utilized is critical if one is to obtain consistently good outcomes. Injecting into the body of the lip will tend to produce volume, while injections into the rolled border will tend to produce definition. Despite a proliferation of the number of products available, the fundamental principles of lip augmentation have not changed. Understanding the patient's goals, observing their anatomy, and individualizing each treatment are essential to successful outcomes when augmenting lips with injectables.

References

1. Klein A. In search of the perfect lip: 2005. *Dermatol Surg* 31(11 Pt 2):1599-1603 (2005 Nov).
2. Carruthers J, Narukar VA. Management of the lips and mouth corners. In: Carruthers J, Carruthers A, editors. *Procedures in cosmetic dermatology series: soft tissue augmentation.* Philadelphia: Saunders (2005).
3. Rohrer T. Soft tissue augmentation. Presented at: the American Society for Dermatologic Surgery Annual Meeting, San Diego, California (2004).
4. Semchyshyn N, Sengelmann R. Botulinum toxin A treatment of perioral rhytids. *Dermatol Surg* 29(5):490-5 (2003 May).

Class	Name/Company	Approval Dates and Comments
Antiacne Agent	**Drospirenone/ Ethinyl Estradiol** *Yaz®* Berlex	The US FDA approved a new indication for this oral contraceptive (OC) in January 2007 to treat moderate acne vulgaris in women who desire an OC for birth control.
Corticosteroids	**Clobetasol Propionate 0.05%** *Olux-E™ Foam* Stiefel Laboratories	The US FDA approved this corticosteroid in January 2007 for the treatment of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses (psoriasis and eczema) in patients ≥12 years of age.

Drug News	
HPV Infections	A study published in a recent issue of the *JAMA**, suggested that about one in four US females between the ages of 14 and 59 years may have the sexually transmitted human papillomavirus (HPV) infection. Prevalence of any HPV infection was highest among females aged 20-24 years (44.8%); and overall HPV prevalence among females aged 14-24 years was 33.8%. However, the prevalence of HPV vaccine types 6 and 11 (low-risk types), and 16 and 18 (high-risk types) was relatively low (only 3.4% of female participants). *Dunne EF, et al. *JAMA* 297(8):876-8 (2007 Feb 28).
Stress and Acne	The largest study ever conducted on acne and stress, recently published in *Acta Dermato-Venerologica** reveals that teenagers who were under high levels of stress were 23% more likely to have increased acne severity. The study involved 94 secondary school students in Singapore with a mean age of 14.9 years. The students' self-reported stress levels and acne severity were measured at two different times – just before mid-year exams and during summer break. Students reporting high stress were 23 percent more likely to have increased severity of acne papulopustulosa. Levels of stress were not linked to severity of acne comedonica. *Yosipovitch G, et al. *Acta Derm Venereol* 87(2):135-9 (2007 Mar).
US FDA Advisory Committee Membership Eligibility	In March 2007, The US FDA announced new draft guidance that would implement a more stringent approach for considering potential conflicts of interest of its advisory committee members and for recommending eligibility for meeting participation. This new guidance (www.fda.gov/oc/advisory/waiver/coiguidedft.html) would reduce the likelihood that the process for recommending waivers would vary from meeting to meeting. In addition to a more streamlined approach for considering who may participate in meetings, the FDA would tighten its policy for considering eligibility for participation. Anyone who has disqualifying financial interests with a combined value exceeding $50,000 after applying certain exemptions, would generally not be considered for participation in the meeting, regardless of the need for his or her expertise. If the financial interests are <$50,000 after applying certain exemptions, the individual might be recommended to participate as a non-voting member. Only individuals with no potential conflicts would be eligible to fully participate in meetings as voting members. The FDA is accepting public comments on the proposal through May 20, 2007.

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