HIGHLIGHTS OF

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Abstract

Updates on managing some of the most common dermatologic conditions for which patients seek care illuminated presentations at the Skin Disease Education Foundation's 42nd Annual Hawaii Dermatology Seminar®. This educational supplement summarizes the highlights of clinical sessions presented during this CME/CE conference.

Treatment of psoriasis has continued to advance, with three interleukin (IL)-17 antagonists approved by the US Food and Drug Administration (FDA) and a fourth in phase 3 trials. An authority on the use of biologics in psoriasis presents current data on the safety and efficacy of these therapies. Tumor necrosis factor (TNF) inhibitors also retain a place in the management of psoriasis, with records of long-term safety. A fourth TNF inhibitor awaits FDA approval for use in psoriasis, offering data on transmission during pregnancy and lactation. An expert on the use of this drug class presents the evidence.

Topical therapies remain the cornerstone of care for many patients with psoriasis as well as those with rosacea. Our faculty update readers about new and investigational topical therapies for moderate or severe psoriasis, as well as for acne and rosacea. The current literature on monitoring patients receiving isotretinoin also is summarized.

Aesthetic and cosmetic dermatology services form a sizable portion of some practices. Our faculty review data on safety of topical and procedural therapies for cellulite as well as safe injection of facial fillers.

Keywords

Acne; adalimumab; adapalene; bimekizumab; brimonidine; brodalumab; cellulite; certolizumab pegol; cosmetic dermatology; doxycycline; etanercept; facial filler injection; halobetasol propionate; IL-17 inhibitors; infliximab; isotretinoin; ivermectin; ixekizumab; minocycline; oxymetazoline hydrochloride; psoriasis; tumor necrosis factor inhibitors; secukinumab; tapinarof; tazarotene; vascular occlusion

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Optimizing Topical Therapy in Psoriasis

Systemic biologic agents have revolutionized care of psoriasis, but topicals remain the mainstay of dermatologic therapy. This article addresses how vehicle affects drug potency, and looks at recent advances in topical therapy.

Vehicle Impacts Drug Penetration and Efficacy A drug's effectiveness depends in part on its delivery to the desired site of action, which is influenced by the vehicle. In one series of studies, betamethasone valerate penetration into the receptor fluid over 24 hours varied with the vehicle. The highest receptor fluid concentration occurred with the ointment formulation, followed by foam and then cream.[1] Adding a second topical therapy can affect receptor fluid concentration of the first agent. Adding tacrolimus ointment to betamethasone valerate cream, for example, enhances the delivery of the steroid compared with betamethasone valerate cream alone. Conversely, adding tacrolimus ointment to betamethasone valerate ointment dilutes both active ingredients, reducing betamethasone valerate delivery compared with betamethasone valerate ointment alone.[1]

Higher steroid potency does not always lead to higher efficacy. A medium-potency steroid (betamethasone dipropionate 0.05%) emollient spray demonstrated efficacy similar to that of a superpotent steroid lotion (augmented betamethasone dipropionate 0.05%) after 2 weeks of therapy in patients with moderately severe psoriasis. The medium-potency agent had a more rapid onset of benefit.[2]

The fixed-combination calcipotriol 50 µg/g and betamethasone dipropionate 0.5 mg/g in aerosol foam provides for fully dissolved active ingredients and has demonstrated significantly higher in vitro skin penetration than the same active ingredients in an ointment.[3] This translates into higher proportions of patients with psoriasis achieving clear/almost clear with ≥2-step improvement (Physician's Global Assessment [PGA]) after 4 weeks of therapy with the foam than with the ointment formulation of calcipotriene 0.005% plus betamethasone dipropionate 0.064% (54.6% and 43.0%, respectively; P=0.025).[4]

Tazarotene-Steroid Fixed Combination for Psoriasis A fixed combination of halobetasol propionate 0.01% and tazarotene 0.045% (HP/TAZ) lotion has been studied in two phase 3 trials in 418 patients with moderate or severe psoriasis. Higher proportions of patients achieved clear/almost clear plus ≥2-grade Investigator Global Assessment (IGA) improvement with the fixed-combination product than with vehicle at week 8 (35.8% and 45.3% with active therapy vs 7.0% and 12.5% with vehicle; P<0.001).[5] A phase 2 study (N=212) had previously demonstrated higher rates of treatment success (clear/almost clear plus ≥2-grade improvement) with HP/TAZ at 8 weeks than with either active agent alone in patients with moderate or severe psoriasis (**Table**).[6]

TABLE Efficacy of Halobetasol Propionate 0.01% and Tazarotene 0.045% in Psoriasis, Phase 2 Study

	N	Proportion achieving primary outcome* at 8 weeks	*P* value vs HP/TAZ
HP/TAZ	59	52.5%	–
HP	63	33.3%	0.033
TAZ	59	18.6%	<0.001
Vehicle	31	9.7%	<0.001

HP, halobetasol propionate 0.01%; TAZ, tazarotene 0.045%; *≥2 grade Investigator Global Assessment improvement and clear/almost clear

Source: Sugarman JL, et al.[6]

Investigational Topicals Tapinarof (GSK2894512). A topical aryl hydrocarbon receptor (AhR) agonist, tapinarof moderates expression of proinflammatory cytokines in human skin.[7] It has been studied for both atopic dermatitis and psoriasis.[8,9]

Janus kinase (JAK) inhibitor. A topical JAK1/JAK2 inhibitor (phosphate 1.0% and 1.5% cream [INCB018424]), applied twice daily for 4 weeks, improved mean lesion scores in patients with psoriasis (n=30).[10]

Maintenance Therapy A major unanswered question in dermatology across conditions is what do to after completing the recommended length of therapy, since the intervention has not cured the disease. Twice-weekly maintenance therapy with clobetasol propionate maintained remission in 75% of 132 patients over an average of 4 months. Side effects were noted in five patients.[11] Pulse therapy with three consecutive doses every 12 hours once a week maintained remission for 12 weeks in 74% (14/19) of those applying betamethasone dipropionate patients and 21% (4/19) of those using vehicle.[12]

A 1-year-long double-blind study of maintenance therapy with calcipotriene/betamethasone dipropionate foam in psoriasis is in progress. Following 4 weeks of active therapy, patients are randomized to twice-weekly maintenance with active therapy or vehicle. Those who relapse are re-treated with the calcipotriene/betamethasone dipropionate foam.

Summary Topical therapy is the mainstay of dermatologic care. Clinicians should consider the vehicle as well as the active agent when choosing treatment and when prescribing multiple topical therapies. Fortunately, there is an active pipeline with new molecules.

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Anti–IL-17 Agents in Moderate to Severe Psoriasis

Medications targeting interleukin (IL)-17 are among the most efficacious options available for treating patients with moderate to severe psoriasis. Secukinumab and ixekizumab each has demonstrated efficacy (Psoriasis Area and Severity Index [PASI] 75, 90, and 100) superior to that of etanercept and ustekinumab.[1-5]

Secukinumab Roughly two-thirds to 82% of patients reached PASI 75 after 12 weeks of therapy with secukinumab 150 mg or 300 mg.[1] Nearly 80% of patients receiving the 300-mg dose reached PASI 90 after 16 weeks of therapy (57.6% with ustekinumab; $P<0.0001$). Half of the patients receiving secukinumab 300 mg reached PASI 75 at week 4, illustrating the early onset of action.[2]

Efficacy and tolerability continued at 5 years, with PASI 75, 90, and 100 response rates of 88.5%, 66.4%, and 41.0%, respectively (with secukinumab 300 mg, the recommended dose for most patients with psoriasis).[6,7] The annual adverse event (AE) incidence rate decreased from 204.6 to 87.2 per 100 subject-years from year 1 to 5; no statistical comparison performed. One death occurred, which was deemed unrelated to treatment. The rate of serious AEs remained stable. Investigators reported no opportunistic infections, two major adverse cardiovascular events (including one deemed unrelated to treatment), three malignancies, nine mild or moderate *Candida* infections, and three cases of ulcerative colitis, including an exacerbation of previous ulcerative colitis.[6] The risk of *Candida* infection is a class effect of IL-17A inhibitors, as this cytokine plays a major role in protecting against this pathogen.[8]

Secukinumab also has demonstrated efficacy in a phase 3 trial for treatment of moderate to severe psoriatic arthritis (PsA) in a phase 3 trial (N=996). From 56% to 63% of patients achieved American College of Rheumatology 20% improvement (ACR20) after 16 weeks, depending on the secukinumab regimen (150 mg or 300 mg with loading dose, 150 mg without loading dose). All secukinumab regimens inhibited radiographic progression over 16 weeks of treatment. Large majorities of patients showed no radiographic progression at week 24 (74% to 88%, depending on the secukinumab regimen). Mean disease activity (Disease Activity Score using C-reactive protein [DAS28-CRP]) and physical function (Health Assessment Questionnaire Disability Index [HAQ-DI]) improved significantly with all secukinumab regimens, compared with placebo.[9]

Ixekizumab Nearly 90% of patients attained PASI 75 at 12 weeks with ixekizumab 80 mg given every 2 weeks after a 160-mg starting dose in the phase 3 trials.[3,4] As with secukinumab, response was rapid; roughly half of patients attained PASI 75 by week 4.[4]

Ixekizumab also has demonstrated superiority to ustekinumab in the treatment of psoriasis (N=302). Nearly three-quarters (72.8%) of patients randomized to ixekizumab achieved PASI 90 after 12 weeks of therapy, compared with 42.2% of those receiving ustekinumab ($P<0.001$). Ixekizumab maintained superior efficacy at week 24 (PASI 75, 90, and 100).[5] Ixekizumab was administered as a 160-mg starting dose, followed by 80 mg every 2 weeks for 12 weeks, then 80 mg every 4 weeks—the US Food and Drug Administration (FDA)-approved dosage for psoriasis.[10] The rate of AEs did not differ significantly by treatment arm. No deaths were reported.[5]

Skin clearing generally was maintained through 60 weeks in an extension trial, in which patients from a phase 3 study received 80 mg ixekizumab every 4 weeks.[3] Long-term efficacy persisted for those receiving ixekizumab every 2 weeks through week 12, then every 4 weeks thereafter (N=385), with 80% of patients reaching PASI 90 and 56% clear (PASI 100) at 108 weeks. Most (85%) treatment-emergent AEs were mild or moderate in severity. About 3.8% of patients developed *Candida* infections. Cerebro-cardiovascular events occurred in 2.4%, malignancies in 1.7%. Less than 1% developed grade 3 or 4 neutropenia (0.6%), Crohn's disease (0.2%), or ulcerative colitis (0.2%). Five deaths occurred, all of which were deemed unrelated to study therapy.[11]

Ixekizumab given every 2 or 4 weeks also has demonstrated efficacy in PsA, with ACR20 rates of 62.1% (dosed at once every 2 weeks) and 57.9% (dosed at once every 4 weeks), compared with 30.2% for placebo ($P<0.001$) and 57.4% for adalimumab (statistical comparison to ixekizumab not performed) after 24 weeks of treatment. It also reduced progression of structural (radiographic) damage compared with placebo, as measured by the van der Heijde modified total Sharp score (mTSS; $P<0.01$). Most patients receiving ixekizumab (89.0% and 94.8%, every 4 weeks and every 2 weeks dosing, respectively) or adalimumab (95.8%) demonstrated no structural disease progression (defined as ≤0.5 change in mTSS at week 24; $P\leq0.001$ vs placebo), compared with 77.4% in the placebo group who attained this milestone. Mean disease activity (DAS28-CRP) and physical function (HAQ-DI) also improved significantly with both ixekizumab doses compared with placebo.[12]

Efficacy in PsA was maintained in an extension trial. Roughly two-thirds of patients continuing ixekizumab once every 2 weeks and once every 4 weeks from the 24-week study demonstrated ACR20 response at 52 weeks (69.1% and 68.8%, respectively).[13]

Brodalumab Unlike secukinumab and ixekizumab, which target the IL-17A subunit, brodalumab blocks the receptor subunit IL-17RA. This may lead to a broader range of potential effects, because multiple ligands (IL-17A, IL-17C, IL-17E, and IL-17F) share this receptor.[14]

Like the other anti–IL-17 agents, this receptor blocker has demonstrated high efficacy in psoriasis; 85% and 86% of patients reached PASI 75 at week 12 with the higher (210-mg) dose, in two phase 3 studies ($P=0.007$ vs ustekinumab in one study). PASI 75 rates at 12 weeks with the lower dose studied (140 mg) were similar to those observed with ustekinumab (67% and 69%, brodalumab 140 mg; 70% and 69%, ustekinumab, two studies) compared with active therapy (ustekinumab). Response (PASI 75) occurred faster with brodalumab than ustekinumab (~4 weeks with brodalumab 210 mg, ~6 weeks with brodalumab 140, ~8 weeks with ustekinumb; $P<0.001$, both brodalumab doses vs ustekinumab). Exposure-adjusted rates of AEs (per 100 patient-years through week 52, two studies) included mild to moderate *Candida* infection (5.2, 5.7), depression (1.7, 1.8), neutropenia (0.2, 1.5), Crohn's disease (0.1, 0.0), serious infections (1.0, 1.3), and serious AEs (8.3, 7.9). Four deaths occurred over 52 weeks among patients receiving brodalumab, due to stroke (one), cardiac arrest (two), and motor vehicle accident (one).[15]

Six completed suicides were documented in patients receiving brodalumab treatment; four of these occurred during the phase 3 psoriasis trial program. In one case, the cause of death was judged indeterminate, because drug overdose was also a possible cause of death. Suicidal ideation also was reported. As a result, brodalumab carries a black box warning for suicide and suicidal ideation; the drug is available only through a Risk Evaluation and Mitigation Strategy (REMS) program. Prescribers and pharmacies must be certified with the program, and patients must sign a patient-prescriber agreement form to receive the drug.[16,17]

Bimekizumab An agent in development, bimekizumab blocks the subunits IL-17A and IL-17F.[18] A phase 2b, dose-ranging trial of this agent reported 12-week PASI 90 response rates of 75.0% and 79.1%, and PASI 100 rates of 60% and 55.8%, for the two highest doses studied.[19] Phase 3 trials are in progress.[20-22]

Inflammatory Bowel Disease and the IL-17 Antagonists All of the agents in this class have been associated with rare onset or

exacerbation of inflammatory bowel disease (IBD).[6,11,15] An analysis recently reported adjudicated IBD cases from the 4,209 patients exposed to ixekizumab in any of seven clinical trials, followed for up to 256 weeks. The incidence rate for Crohn's disease and ulcerative colitis was 1.1 and 1.9 per 1,000 patient-exposure years, respectively. A total of 19 patients were judged to have probable or definitive IBD-related AEs; 15 of those were newly diagnosed with IBD and four experienced flares of known IBD. Eleven of 19 patients stopped ixekizumab therapy because of IBD-related AEs. Of the 16 patients who reported a history of IBD, four had an IBD treatment-emergent AE. Overall, IBD cases were uncommon (<1%) in this clinical trial population.[23]

Summary The anti–IL-17 compounds have substantially advanced therapy for psoriasis, with sizable proportions of patients achieving efficacy endpoints of 90% or 100% clear after 12 weeks of treatment. All three FDA-approved agents in this class have demonstrated efficacy superior to that of active comparators (etanercept and/or ustekinumab) in psoriasis.[1,3,4,15] Secukinumab and ixekizumab have shown efficacy compared with placebo in psoriatic arthritis.[9,12]

Monitoring should include surveillance for AEs of special interest, including opportunistic and serious infections, *Candida* infection, IBD, cardiovascular disease, and malignancy. These events occurred uncommonly or rarely in clinical trials.[6,11,15,23] Brodalumab blocks a receptor rather than neutralizing a subunit and thus has the potential for broader effects than secukinumab and ixekizumab. It is contraindicated in patients with Crohn's disease, has been associated with completed suicides and suicidal ideation, and can be prescribed only through a REMS program.[16]

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Anti-TNF Therapy for Psoriasis

The tumor necrosis factor (TNF) inhibitors, the first biologics approved for psoriasis therapy that are still in use, continue to play a key role in treatment. This article offers an update on the use of TNF inhibitors in psoriasis therapy.

Certolizumab pegol, a TNF inhibitor available for other indications, has recently been studied in psoriasis. At week 16, at least three-quarters of patients achieved PASI 75—75% improvement in Psoriasis Area and Severity Index—with 400 mg once every 2 weeks (75.8% and 82.6%) and at least two-thirds reached PASI 75 with 200 mg once every 2 weeks (66.5% and 81.4%), in two phase 3 trials. Efficacy was well maintained at week 48 for both doses (87.1% and 81.3%, higher dose; 67.2% and 78.7%, lower dose) among subjects who were initial responders and continued on drug.[1] Infections were common, consistent with other biologic therapies (50% and 53% of patients, lower and higher dose, respectively). Most frequently, they were upper respiratory infections and nasopharyngitis. Two serious infections and no opportunistic infections were reported.[1]

Certolizumab pegol uses an antibody fragment (Fab′) conjugated to polyethylene glycol (PEG); it does not contain a fragment crystallizable (Fc) region. This characteristic may account for the minimal transfer of certolizumab from mother to infant during pregnancy,[2] because the neonatal Fc receptor mediates immunoglobulin G transport from the mother to the infant. Among 14 infants whose mothers were treated with certolizumab pegol during pregnancy, 13 had no quantifiable drug levels at birth and one had a minimal drug level at birth. Three of 15 umbilical cord samples had quantifiable certolizumab pegol levels (≤0.048 μg/mL).[2] Minimal transfer through breast milk also has been documented.[3]

TNF Inhibitors in Pediatrics Etanercept has demonstrated long-term safety and efficacy in children and adolescents with moderate to severe psoriasis. During a 5-year, open-label extension study, no opportunistic infections and one treatment-related

serious adverse event (AE) were reported. The most common AEs were upper respiratory tract infection (37.6%), nasopharyngitis (26.0%), and headache (21.5%). PASI 75 rates remained at 60% to 70%, with PASI 90 rates of 30% to 40%, through week 264.[4]

Weight-based adalimumab (0.8 or 0.4 mg/kg, once every 2 weeks) demonstrated superior efficacy and similar safety to weight-based oral methotrexate (0.1-0.4 mg/kg) over 16 weeks in a phase 3 trial in 114 children and adolescents.[5] Higher-dose, but not lower-dose, adalimumab demonstrated efficacy superior to that of methotrexate at 16 weeks (PASI 75 rates of 58%, 44%, and 32%, higher-dose adalimumab, lower-dose adalimumab, and methotrexate, respectively; *P*=0.027 for higher-dose adalimumab vs methotrexate). Infections, the most frequently reported AEs, occurred in 45%, 56%, and 57% of the patients treated with higher-dose adalimumab, lower-dose adalimumab, and methotrexate, respectively.[5]

TNF Inhibitors and Malignancy A year or more of TNF inhibitor therapy has been associated with a statistically significantly higher risk of malignancy (odds ratio [OR], 1.54; 95% CI, 1.10-2.15; *P*=0.01), compared with no anti-TNF therapy.[6] This finding comes from a case-control study of participants in Psoriasis Longitudinal Assessment and Registry (PSOLAR). PSOLAR, sponsored by Janssen,[7] includes patients who received or were candidates to receive systemic therapy (including phototherapy) for psoriasis. A total of 252 patients with newly diagnosed malignancy since registry entry (other than nonmelanoma skin cancer [NMSC]) and 1,008 controls were included. Neither methotrexate nor ustekinumab therapy was associated with increased risk of malignancy.[6] This finding is consistent with an analysis of data from patients receiving anti-TNF therapy for rheumatoid arthritis. That study revealed a higher risk for melanoma and NMSC associated with infliximab and etanercept therapies.[8]

Does Anti-TNF Therapy Reduce Cardiovascular Risk? Researchers have speculated that the elevated cardiovascular (CV) risk associated with psoriasis results from underlying inflammation.[9] In theory, anti-inflammatory treatment for psoriasis may ameliorate CV risk. A claims data analysis (2000-2011) compared the risk of major CV events among adults with psoriasis receiving TNF inhibitors or methotrexate.[10] TNF inhibitor therapy was associated with reduced risk of major CV events in patients with psoriasis (Kaplan-Meier 12-month rates of major CV events, 1.45% and 4.09% for TNF inhibitor therapy and methotrexate, respectively; P<0.001).

Summary TNF inhibitors remain a relevant option for psoriasis, offering years of safety data in pediatric as well as adult patients, possible reduction in cardiovascular risk, and data about the risk of malignancy. A TNF inhibitor recently studied for psoriasis has documented minimal transmission during pregnancy and lactation.

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What's New in Acne

Topics covered in this literature review include the frequency of laboratory monitoring and surveillance for rhabdomyolysis during isotretinoin therapy; an alternative therapy for patients with severe acne; the association of diet and acne; and investigational therapies.

Laboratory Monitoring During Isotretinoin Therapy Guidance regarding the frequency of laboratory monitoring during isotretinoin therapy has changed over the years. The package insert recommends baseline fasting lipid and hepatic panels with repeated testing at weekly or biweekly intervals until "the response has been established."[1] One recent report found no mean difference in complete blood count (CBC), hepatic panels, and lipid panels between weeks 8 and 20.[2] Another reported that hypercholesterolemia and/or alanine tranaminitis were detected after a mean of 50 and 62 days of therapy, respectively.[3] This study found no need to measure CBC.[3] Both of these reports concluded that there is no basis for laboratory monitoring after 2 months, in the absence of abnormal findings or a dosage change.[2,3]

Elevated aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels were frequently accompanied by elevated creatine kinase (CK) in one analysis, suggesting that the abnormal ALT and AST findings may have reflected muscle rather than liver damage. The investigators suggest that gamma-glutamyl transferase (GGT) is more relevant than ALT and AST for monitoring liver function. Multiple CK elevations were common (57/246), especially in males (56/57 with multiple CK elevations).[4]

Based on these findings, in our practice we monitor GGT rather than ALT and AST; we follow CK (particularly in males); and we do not monitor CBC. We perform laboratory tests at months 1 and 3 and any time the isotretinoin dose is increased or if patients alter their exercise routine.

Detecting Rhabdomyolysis During Isotretinoin Therapy Rhabdomyolysis is rarely reported in patients taking isotretinoin; when it occurs, it generally is associated with strenuous physical activity.[1] Research suggests that exercise and isotretinoin can act synergistically to raise CK levels.[5,6]

Not all CK elevations herald rhabdomyolysis, however. Moderately intense exercise with muscle contractions (eg, weight lifting or downhill running) can raise CK to levels associated with rhabdomyolysis without causing renal dysfunction.[7]

CK elevations substantially exceeding 11 times the upper limit of normal have been associated with rhabdomyolysis, along with muscle symptoms, pigment nephropathy, and brown urine with myoglobinuria.[8] Yet CK elevations following strenuous exercise vary widely, as do CK values associated with rhabdomyolysis.[8] Patients with myalgia, weakness, and dark urine along with CK elevations should be followed closely, with findings evaluated in the context of patient history and exercise habits.[8] CK increases tend to be more common and more pronounced in males,

those of black race, and untrained individuals (eg, "weekend warriors").

Our center measures CK before starting isotretinoin in all patients who are athletic. This is especially important in males, given the fact that reports of elevated CK are more common in males than females. Patients are asked to note their exercise the day before and after follow-up blood tests. Those with a CK ≥1,000 IU/L are contacted with advice to drink more water and reduce exercise for a few days.

An Alternative to Isotretinoin Therapy A 12-week, open-label, multicenter study demonstrated that adapalene 0.3%/benzoyl peroxide 2.5% (ADAP 0.3%/BPO 2.5%) gel plus oral doxycycline 200 mg/day is efficacious in patients with severe inflammatory acne (Investigator Global Assessment [IGA] 4) who are candidates for isotretinoin (N=186). The inflammatory lesion count decreased significantly from baseline, with a mean reduction of 66.2% (P<0.0001). More than one-third (37%) of patients achieved scores of clear/almost clear at week 12.[9]

Isotretinoin-Induced Acne Fulminans Eruption of acne fulminans (ulceration, crusting, and scarring) during isotretinoin therapy is most common in teenage males with acne prominence on the back and chest. It usually is not accompanied by systemic symptoms.[10]

Experts at a consensus conference recommend discontinuing isotretinoin and initiating systemic corticosteroids (<0.5-1 mg/kg/day) to gain immediate control of inflammation, until crusted lesions have healed.[10] Low-dose isotretinoin (0.1 mg/kg/day) can be added and overlapped with a steroid taper. The isotretinoin dose can be increased as the steroid dose is decreased. Starting isotretinoin at a low dose (<0.5 mg/kg/day) may reduce the risk of acne fulminans.[10]

A New Formulation of Doxycycline A new delayed-release formulation of doxycycline hyclate tablet has a modified polymer enteric coat that increases acid resistance[11] and further delays absorption by 10 to 15 minutes, thereby decreasing associated gastrointestinal distress.

Investigational Therapies Topical minocycline gel. A phase 2b, 12-week-long, dose-ranging trial of a topical minocycline gel (1% and 2% vs vehicle) in patients with moderate or severe inflammatory acne has been completed; at the time of this writing, results have not been published.[12] Preclinical studies showed no detectable concentrations in plasma.[13]

Topical minocycline foam 4%. This agent reduced absolute inflammatory lesion count significantly more than a foam vehicle in two identical 12-week phase 3 studies (N=466, N=495). Only one of these studies reported significant findings on the other coprimary endpoint (IGA score of clear or almost clear plus at least a 2-grade improvement from baseline [active therapy vs vehicle: 14.7% vs 7.9%; P=0.04; 8.0% vs 4.7%; P = 0.22]).[14]

Oral sarecycline. A once-daily tetracycline-class antibiotic, sarecycline 1.5 and 3.0 mg/kg generated significantly greater reduction in inflammatory lesion counts at week 12 compared with placebo (by 52.7%, 51.8%, and 38.3%, respectively) in a phase 2 trial of 285 patients with moderate or severe acne. Rates of gastrointestinal adverse events were similar to those of placebo.[15]

Topical olumacostat glasaretil (OG) 7.5%. This topical sebum inhibitor did not meet its coprimary endpoints in two phase 3 trials. Development is not proceeding at the time of this writing.

Diet and Acne A recent study demonstrated that consumption of milk is associated with acne.[16] Nonfat and low-fat milk, but not full-fat milk or total dairy consumption, were significantly associated with acne in teens 14 to 19 years old (N=225). An earlier study in teenage boys (N=4,273, prospective cohort) reported similar findings.[17] Conversely, a study in teen girls (N=6,094, prospective cohort) linked the risk of acne to consumption of total milk and whole milk, as well as low-fat and skim milk.[18] Consumption of dietary carbohydrates (higher total and as a percentage of energy intake, as well as glycemic load) also has been linked to the rate of moderate/severe acne.[19]

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Rosacea: An Update

Recent research continues to elucidate the role of inflammation in rosacea and its association with other diseases. New therapies include topical minocycline, the alpha-adrenergic receptor agonist oxymetazoline, and the antiparasitic/anti-inflammatory agent ivermectin used alone and concurrently with or before brimonidine therapy.

Doxycycline: Clinical Results Correlate With Biomarkers Evidence suggests that doxycycline efficacy in rosacea correlates with changes in biomarkers.[1] Attaining clear/almost clear (Investigator Global Assessment [IGA] score 0 or 1) at week 12 with doxycycline was correlated with reduced levels of cathelicidin protein in the stratum corneum in adults with papulopustular rosacea. Doxycycline treatment also was associated with inhibition of mRNA of kallikrein 5 and cathelicidin antimicrobial peptide at week 12 compared with baseline (difference vs placebo, P<0.01), as well as a decrease in kallikrein and matrix metalloproteinase activity at week 2 compared with baseline (difference vs placebo, P<0.01).[1]

Inflammation in Rosacea: More Than Skin Deep? Studies published over the last 5 years have detected an association between

rosacea and Parkinson's disease,[2] glioma,[3] dementia,[4] depression and anxiety disorders,[5] allergies,[6] various gastrointestinal diseases (celiac disease, Crohn's disease, gastroesophageal reflux disease, ulcerative colitis, and irritable bowel syndrome),[6-9] metabolic diseases,[6] urogenital diseases,[6] female hormone imbalance,[6] and multiple autoimmune diseases in women (type 1 diabetes, multiple sclerosis, and rheumatoid arthritis).[10] Some evidence suggests an association with cardiovascular risk factors,[11,12] although other studies have not found a linkage with cardiovascular disease.[13,14] Evidence for an association of rosacea with ulcerative colitis is mixed.[9]

Treatment: Topical Minocycline Foam In a phase 2 study of patients with papulopustular rosacea, topical minocycline foam 1.5% and 3% each reduced the inflammatory lesion count from baseline to 12 weeks significantly more than vehicle ($P<0.001$). Efficacy rates with the two concentrations did not differ significantly; phase 3 studies are evaluating the lower concentration.[15,16] A topical minocycline gel (1% and 2% concentrations) also is being studied in rosacea.[17]

Oxymetazoline Hydrochloride Cream 1% In two pivotal studies, roughly 12% to 18% of patients achieved at least a 2-grade improvement in clinician and patient self-assessment on day 29 of therapy ($P\leq0.001$ vs vehicle, both studies). Participants had moderate to severe facial erythema of rosacea at baseline.[18,19] The rate of treatment-related adverse events (TRAEs) during the two 29-day studies was 6.3% and 8.5% with active therapy and 5.1% and 5.0% with vehicle. No treatment-emergent adverse event, related or not, was observed in more than 3.1% of patients in either study.[18,19]

Anti-inflammatory/Antiparasitic Agent: Ivermectin Approximately 40% of patients with moderate to severe papulopustular rosacea achieved clear/almost clear after 12 weeks of therapy with ivermectin 1% cream once daily at bedtime, in two randomized, double-blind, vehicle-controlled studies ($P<0.001$ vs vehicle).[20]

A 16-week study compared ivermectin 1% cream once daily to metronidazole 0.75% cream twice daily in patients with moderate or severe papulopustular rosacea. Percentage reduction from baseline in inflammatory lesion counts (primary endpoint) was significantly larger with ivermectin than with metronidazole at week 16 (83.0% and 73.7%, respectively; $P<0.001$). A higher proportion of patients achieved clear/almost clear with ivermectin (84.9% and 75.4%, respectively; $P<0.001$).[21]

To ascertain time to relapse, patients who attained clear/almost clear during the 16-week trial discontinued therapy and were followed for another 36 weeks. Remission duration was significantly longer in patients who had used ivermectin. Median time to first relapse (IGA ≥2) was 115 days following ivermectin therapy and 85 days in those who had received metronidazole. Relapse rates at 36 weeks after treatment discontinuation were significantly lower in those who had received ivermectin (62.7% and 68.4%, ivermectin and metronidazole, respectively; $P=0.04$).[22]

Post hoc analysis indicated that, regardless of which active therapy was used, treating to clear rather than almost clear in the 16-week trial reduced the risk of relapse (**Figure**).[22]

Ivermectin's efficacy in rosacea has been associated with both antiparasitic and anti-inflammatory actions. In patients with moderate or severe papulopustular rosacea at baseline, 6 and 12 weeks of ivermectin therapy significantly reduced the mean density of Demodex spp mites on the skin ($P<0.001$) and also decreased the expression of various inflammatory markers (interleukin-8, LL-37, human β-defensin 3, and tumor necrosis factor-α) at those time points. All 20 patients improved clinically, and 16 achieved IGA clear/almost clear.[23]

Ivermectin and Brimonidine: Sequentially or Concurrently? Anti-inflammatory therapy is recommended for papulopustular rosacea, and alpha-adrenergic agonists are used for facial erythema associated with rosacea. In patients with both manifestations, should these agents be given concurrently or should the anti-inflammatory agent be started first? A study evaluated this question by comparing a regimen in which topical ivermectin and brimonidine were initiated at the same time to a regimen in which ivermectin was started 1 month before brimonidine. Each of these regimens was compared with two vehicles. Starting both active therapies at the same time was associated with improved efficacy. At week 12, rates of clear/almost clear 3 hours after brimonidine application were 61.2%, 50.0%, and 36.8% for the groups that started both active therapies at the same time, those delaying brimonidine by 1 month, and the two vehicles, respectively. Only the first treatment group (simultaneous initiation) demonstrated efficacy significantly higher than that of the two vehicles ($P=0.003$).[24]

Also of interest is that the proportion of patients attaining 100% reduction in inflammatory lesions was higher among those starting both active therapies at the same time compared with the two vehicles (16.3%, 6.5%, and 4.2% at week 12; simultaneous initiation, 1-month delayed brimonidine, and two vehicles, respectively; $P=0.015$ for simultaneous initiation vs two vehicles). Yet both groups received ivermectin for 12 weeks. The rate of TRAEs was lower with active therapy (4.2%) than with brimonidine monotherapy (~10%).[24,25]

Summary The central role of inflammation in the pathophysiology of rosacea is underlined by the finding that treatment success with the antibiotic doxycycline is associated with reduction of biomarkers associated with inflammation in rosacea. New approaches to therapy include topical minocycline foam and gel as well as the antiparasitic/anti-inflammatory agent ivermectin, given alone or in combination with an alpha-adrenergic receptor agonist to address facial erythema.

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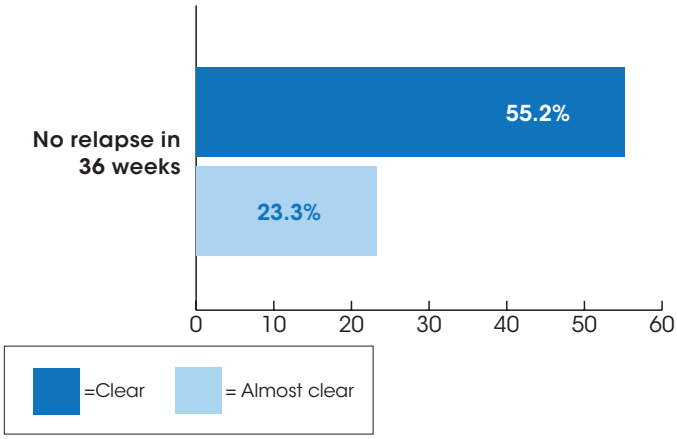
FIGURE Effect of Treating to Clear vs Almost Clear in Rosacea



A post hoc analysis demonstrated that treating to clear rather than almost clear in a 16-week clinical trial reduced the risk of relapse during a treatment-free, 36-week follow-up period, regardless of therapy used during the trial. Patients were treated with ivermectin 1% cream once daily or metronidazole 0.75% cream twice daily for 16 weeks. Clear, n=270; almost clear, n=487.
Source: Taieb A, et al.[22]

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Safety When Injecting Facial Anatomy

Injection of fillers is the second most common minimally invasive cosmetic procedure in the United States, with an estimated 2.6 million injections of soft tissue fillers performed in 2016.[1] Filler injections are generally well tolerated, with mild and transient side effects such as erythema, bruising, tenderness, and swelling.[2] A potentially serious complication is arteriovenous occlusion, which can result from injecting filler into a vessel or compression of the vessel from filler material externally placed. Vascular occlusion causes tissue ischemia, which can lead to skin necrosis, scarring, and less commonly vision loss, hemiplegia, or stroke.[2,3]

An intimate knowledge of facial anatomy is crucial for safe injection and mitigation of untoward side effects. While adverse toxin effects usually involve adjacent muscle paresis, adverse filler effects relate more to vascular events. This article focuses on safe injection practices for fillers.

Immediate signs and symptoms of vascular injury during filling include pain, blanching, ecchymosis, or a flash of blood during reflux or even needle removal. Delayed signs include pain or achiness, dusky discoloration, reticulate erythema, and skin breakdown.[2-4] Signs of impending vision loss following filler treatment include eye pain, headache, dizziness, reduced vision, ptosis, nausea, and ophthalmoplegia.[3]

A review of 98 cases of vision complications following filler injection concluded that the most common injection sites associated with this adverse event were the forehead, glabella, nose, and nasolabial folds.

FIGURE 1 Blood Supply to the Glabella

The supratrochlear and supraorbital arteries supply the glabella.

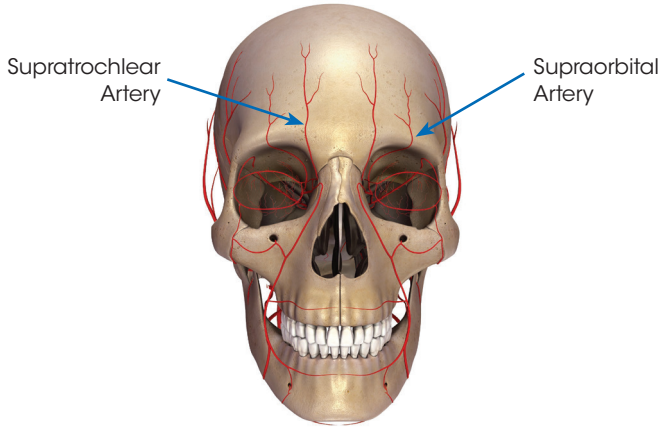
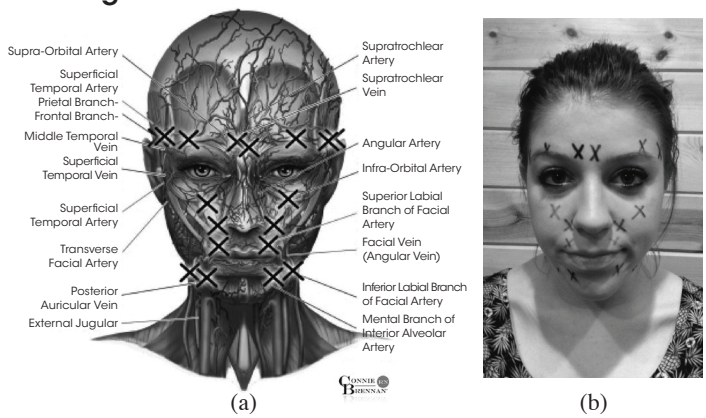


Illustration of the blood supply to the glabella. Note the distribution of the supratrochlear and supraorbital arteries.

FIGURE 2 Facial Arterial-Venous System and "Danger Zones"



(a) The facial arterial/venous system and "danger zones" (black X's); (b) Model with "danger zones" (black X's) identified.

Source: Used with permission. Brennan C. *Plast Surg Nurs.* 2014;34(3):108-111.[5]

TABLE 1 Preventing Vascular Occlusion: General Suggestions

- Use a well-lit space
- The patient's head should be upright and laid on the headrest
- Protect the patient's eyes
- Mark visible vessels prior to injecting
- Reflux prior to injecting; if blood enters the syringe, do not inject filler
- Consider using a blunt tipped cannula when possible
- Inject slowly, in retrograde fashion
- Use a low-pressure syringe (<1-cc syringe) and larger caliber needle in deeper planes to minimize injection force
- In superficial dermis, use the smallest possible needle and note extrusion of product through adjacent pore
- Inject small aliquots, 0.05-0.2 cc/thread or depot, especially in high-risk areas
- Always move needle or cannula
- Observe the patient for signs of distress or possible vascular occlusion
- Have nitroglycerin paste and hyaluronidase easily accessible in the surgical space in case of need
- Teach office staff to triage calls and immediately refer patient reports of pain or unilateral swelling to a licensed provider
- Establish relationships with ophthalmologists, oculoplastics, and neurology colleagues who will examine patients in an emergency, should complications develop

Beleznay K, et al. *Dermatol Surg.* 2015;41:1097-1117.[3]

TABLE 2 Management of Vascular Occlusion/ Impending Skin Necrosis[3,4]

Immediate

- Warm compresses
- Massage, tap the area
- Aspirin
- Normal saline/hyaluronidase lavage
- Topical nitroglycerin under occlusion to increase vasodilation

If vision deficit occurs

- Call ophthalmologist for urgent consult for slit lamp evaluation of retinal vessels
- Typically irreversible

Close follow-up and consider

- Low-molecular-weight heparin for 14 days
- Corticosteroids
- Antibiotics
- Hyperbaric oxygen therapy
- Obtain a second opinion

Beleznay K, et al. *Dermatol Surg.* 2015;41:1097-1117.[3]
Hirsch RJ, et al. *Dermatol Surg.* 2007;33:357-360.[4]

Vision complications occurred rarely following injections in most parts of the face, including the temporal region, lips, and chin.[3] Following are suggestions based on the literature and Dr. Sengelmann's practice experience for safe injection in these specific areas. **Tables 1 and 2** offer general guidance for preventing and managing vascular occlusion.

Mid-forehead and Glabella *Vascular anatomy.* Small branches of the supratrochlear and supraorbital arteries feed these areas, with little collateral circulation ("watershed area"; **Figure 1**).[2]

Suggested technique. Inject superficially into the dermis with extrusion or deeply over the periosteum, in a blood-free plane.

Temporal Area *Vascular anatomy.* The temple, tail of brow, and lateral canthus are served by the superficial and middle temporal arteries (**Figure 2**).[5] The periorbital vasculature is also located in this region.

Suggested technique. Prior to injecting the tail of brow or temple, push at the zygoma and mark any vessels that surface. Inject deeply over bone, under muscle. Alternatively, one can inject just subdermally using a cannula. Superficial intradermal injections are laborious but also useful for discreet skin rhytids.

Tear Trough, Lateral Orbital, Periorbital Areas *Vascular anatomy.* The angular artery (**Figure 2**), palpebral artery (upper lid), and zygomatico-orbital artery (lateral tear trough).

Suggested technique. A favored technique is to inject below the orbicularis oculi and above the periosteum. Minimize the number of passes. Consider using a blunt tipped cannula when injecting. This is especially important when one is injecting subdermally where vasculature is copious. In so doing, an 18-gauge cannula is used to puncture the skin, followed by a 25-gauge cannula to thread the filler superficially under the dermis. Protect the globe and inject above the bony rim. Take care not to injure the globe or penetrate the orbital septum, behind which are larger-caliber vessels and orbital fat pads. Small volumes in the orbit (average, 0.1-0.2 mL per injection thread) are recommended.

Nasolabial Fold *Vascular anatomy.* The facial artery and the angular artery (**Figure 2**).[5,6]

Suggested technique. Inject into an immediately subdermal plane. "Hug" the dermis with the needle. Be aware that the angular artery can include tortuous, superficial curves.[4] If the goal of treatment is to volumize and lift the midface, then inject down on the periosteum into Ristow's space (at the most superior aspect of the nasolabial folds and lateral to the nasal ala) with a cannula using depot technique. I favor a cannula for this approach and use only small depots until the desired results are achieved.

Lips *Vascular anatomy.* The labial artery, superior and inferior branches, are tortuous vessels in the pink lip and the upper cutaneous lip.

Suggested technique. For fine lines, inject the superficial dermis with a serial puncture technique so as not to enter the subcutaneous tissue. Entering the subcutaneous tissue could cause volume instead of rhytid effacement. Inject the vermilion border in the potential space between cutaneous lip and mucosa. Minimize threading and use a slow injection technique.

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Aesthetic Medicine: Treating Cellulite

Cellulite is characterized by a dimpled appearance of the skin—typically in the buttocks and thighs—in which the dermis is tethered by subcutaneous fibrous septae perpendicular to the skin surface.[1,2] Other characteristics of cellulite include striae, laxity, and elevated areas. It is considered a normal physiological state in women who are past adolescence, as approximately 85% to 90% of women over the age of 20 have some degree of cellulite. It is thought that the hormonal milieu of puberty fosters the development of cellulite in women. Hormones are thought to play a central role in the pathophysiology of cellulite, which typically worsens with pregnancy, hormonal contraception, and hormone replacement therapy.[1]

Imaging studies have identified differences in the skin structure of women with cellulite as compared both with women without cellulite and with men. Women with cellulite have a higher percentage of fibrous septae oriented perpendicular rather than parallel to the skin surface, compared with men and with women without cellulite, whose fibrous septae are oriented obliquely or parallel to the skin surface.[3] Raised areas result from the projection of fat to the skin surface.[4] These alterations in connective tissue produce the bumpy appearance associated with cellulite.[1,5]

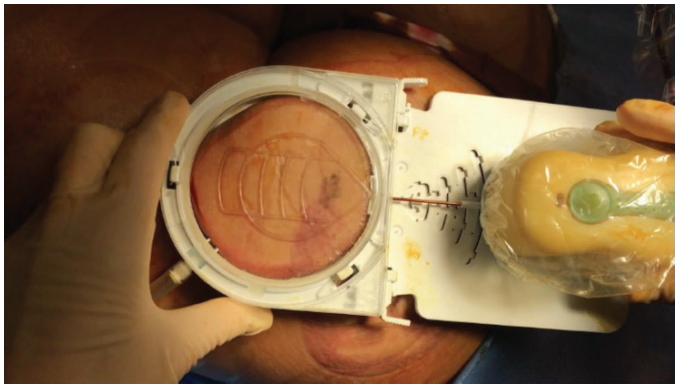
Treatments Topical retinol. In a small study (N=15), skin elasticity increased by 10.7%, and viscosity decreased by 15.8%, after 6 months of topical retinol treatment.[6] Topical treatments for cellulite all seek to strengthen the "roof," or skin surface, thereby improving the rippled appearance.

Laser subcision. A three-step treatment with a 1440-nm side-firing Nd:YAG laser was studied in 15 women with moderate to severe cellulite (Cellulaze™; Cynosure, Inc.). Treatment involved aiming the laser fiber deeply to debulk fat, orienting the fiber parallel to the skin surface to thermally subcise the septae, and pointing the fiber toward the undersurface of the skin to induce dermal remodeling and skin tightening. Mild ecchymosis and edema resolved about 2 weeks post procedure, with no other adverse events reported. Average patient and investigator satisfaction was 4.1/6 and 5.2/6, respectively, at 3 months, and 4.9/6 and 5.0/6 at 6 months.[7] Although this cellulite treatment has been successful in the hands of expert clinicians, it has not been widely adopted.

Tissue stabilized-guided subcision (TSGS). Another system that targets dimples and short horizontal lines of cellulite employs a vacuum-assisted tissue capture platform to provide precise control of the depth and area of tissue release (Cellfina®; Merz North America). A vacuum chamber lifts and fixes the tissue for the anesthesia needle or tissue release microblade, minimizing operator variability (**Figure**).[2] In the pivotal trial, 55 women with moderate to severe cellulite received a single TSGS treatment. The mean baseline Cellulite Severity Scale (CSS) score of 3.4 (0 to 5) decreased significantly to 1.3 at 3 months and 1.4 at 1 year post procedure ($P<0.0001$). Patient satisfaction scores indicated that, although 100% of subjects were unsatisfied to very unsatisfied at baseline, 85.5% reported being satisfied or very satisfied at 3 months, and 100% rated themselves satisfied or very satisfied at 1 year.[2] The most common treatment-related adverse effects were ecchymosis (n=37), hemosiderosis (n=19), and soreness (n=19). Follow-up evaluation 3 years after the single treatment revealed treatment benefits persisted with no recurrence of cellulite.[8]

Improving Skin Laxity Skin laxity increases with age, potentially worsening the appearance of cellulite. Radiofrequency, infrared light, and acoustic wave therapy are among the noninvasive, energy-based interventions to address this condition.[4] Microfocused ultrasound with visualization followed by injection of diluted calcium hydroxylapatite (CaHA) significantly improved the CSS ($P<0.001$) in 20 women with skin laxity and moderate to severe cellulite. Treatment effects of erythema, edema, and bruising were rated as mild and resolved within a few days. Most women (19/20) rated themselves as satisfied or very satisfied with treatment results 90 days post procedure.[9]

FIGURE Tissue Release During Tissue Stabilized-Guided Subcision



Marked cellulite dimple is captured in the vacuum platform. The reciprocating microblade is inserted into the skin, and the motor module is guided through the arc of the treatment platform to subcise the fibrous septae.

Photo courtesy of Jeremy B. Green, MD.

Summary Cellulite is a normal, common phenomenon among adult women that can nonetheless cause considerable distress. Treatment options include topicals such as retinol, noninvasive energy-based devices to tighten the skin, laser-based subcision, and tissue stabilized-guided subcision. On the horizon, an injectable collagenase drug to target fibrous septae is in phase 3 trials.[10,11] Additionally, there is increasing interest in utilizing dilute biostimulators like CaHA and poly-L-lactic acid to induce neocollagenesis and improve skin quality in individuals with cellulite.[12]

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