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A Review of Systemic Retinoid Therapy for Acne and Related Conditions

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ABSTRACT

Oral isotretinoin, since its introduction more than 20 years ago, has been and still is the "gold standard" in the treatment of acne and its variants. This is the only approach to acne with the possibility of a permanent "cure" or long term remission. The role of isotretinoin has evolved with higher dosage schedules and use earlier in the course of the disease. The frequency of laboratory monitoring has diminished along with associated costs based on 2 decades of experience. Pregnancy-associated safeguards have become a more prominent facet of oral retinoid therapy leading to increased safety for its use in females of child-bearing potential.

KEY WORDS: *acne, isotretinoin, retinoids*

Isotretinoin (13 cis-retinoic acid, Accutane®, Roaccutane®, Roche Pharmaceuticals) is a naturally occurring substance which, since its introduction in 1982, has revolutionized acne therapy. It is the only anti-acne agent that affects all four of the known major etiologic mechanisms: sebum production, comedogenesis, *Propionobacterium acnes* (*P. acnes*) colonization of ductal and skin surface, and monocyte chemotaxis-induced inflammation. This may explain its unique ability to sustain long term treatment-free remissions and, in some cases, a permanent remission or "cure" can be achieved.[1,2]

Indications

Initially with the introduction of isotretinoin, only patients with severe nodular cystic acne or severe inflammatory acne, who were not responding to conventional therapy were given the drug. Now, with more than 20 years of treatment experience, expanded guidelines for its use include:[3-5]

- Moderate acne relapse (<50% improvement) after a single adequately-dosed course of antibiotics or hormonal therapy of 4 months
- Significant psychosocial impairment
- Marked concomitant seborrhea
- Gram negative folliculitis
- Scarring or persistent dyschromia

Not only deep nodular, but also superficial inflammatory acne can result in scarring. Because scarring is frequently missed during examination, proper assessment of scarring is paramount and was well described in a recent publication.[5]

Isotretinoin is also of benefit for patients with persistent adult acne who have suffered for many years, or whose acne flares when adequate conventional therapy has been discontinued. Acne persisting into the 6th and 7th decades, termed "pensioners' acne" has been treated with low dose (0.25mg/kg/day) or intermittent 1 week in every 4 schedules.[6-8]

Acne conglobata is certainly the best indication for isotretinoin therapy; however acne fulminans, after initial "calming" of the exacerbation with oral tapering dose steroids over 4-6 weeks, responds

well to the retinoid.[9] Gram-negative folliculitis can be effectively treated not only with ampicillin, co-trimoxozole or trimethoprim, but with isotretinoin as well.[10,11]

Hidradenitis suppurativa and rosacea patients have benefited from isotretinoin therapy as well.[3] Isotretinoin is used in pyoderma faciale after initial oral steroids for the first 4 weeks. It has not shown benefit in vasculitic acne, which is usually treated with oral steroids, azathioprine or cyclosporine.[12] Acne excoriee is often quelled with a course of isotretinoin. Good results have been reported in its use for granulomatous perioral dermatitis.

Contraindications

Parabens allergy is a contraindication to oral therapy with isotretinoin because parabens is an excipient in the medication. Due to the "retinoid syndrome" of potential birth defects, pregnancy is an absolute contraindication. With this in mind, the manufacturer has developed the Pregnancy Prevention Program™. This program educates the female patient about the need for two effective methods of contraception and avoidance of pregnancy during treatment and for 1 month after therapy termination.

Although the pregnancy rate has decreased to 0.003% in the US according to the 2001 Slone Accutane® Epidemiology Database, the absolute number of pregnancies has not decreased due to increased number of prescriptions. Analysis of the Slone data show that the patient most likely to have an Accutane® exposed pregancy is a 26 year old woman. In order to address these concerns, as of April 2002, in the US, this program has evolved into the SMART™ Program (System to Manage Accutane Related Teratogenicity) developed by the manufacturer and the US FDA.[13]

Relative contraindications to isotretinoin therapy with appropriate dosage adjustments are outlined by Cunliffe and Stables.[12]

Dosage

Acne therapy is usually initiated at a dose of 0.5mg/kg daily for the first 2-4 weeks and then increased to 1.0mg/kg/day for the remainder of the 20 week course. Upon initial introduction in 1982, lower dosages of 0.1-0.5mg/kg/day were given for severe acne with data analysis showing increased rates of recurrence compared to the dosages recommended today.[1] The minimum total cumulative dose associated with long term, permanent remission is 120mg/kg. Some patients requiring re-treatment after relapse or partial response may require doses of 1.5-2.0mg/kg/day.[14] Dermatologists often continue treatment until the patient is clinically clear, although there is controversy regarding benefits beyond 150mg/kg.[1] Doses must be adjusted in some cases of concomitant systemic disease. (See Table 1).

Inflammatory acne flare is experienced by approximately 6% of patients in the first month of therapy, and is clinically significant in about half.[15] Discontinuation of isotretinoin and initiation of therapy with prednisone at 0.5-1.0mg/kg/day for 2-3 months is the treatment of choice.[5]

Similar doses to those used in acne are given in acne variants such as mature acne, acne conglobata, Gram-negative folliculitis, pyoderma faciale and hidradenitis suppurativa and dissecting cellulitis of the scalp.[12]

A lower initial dose of 0.25mg/kg/day of isotretinoin, increasing to 1.0mg/kg/day at the end of the 6th week are recommended for acne fulminans, after a course of prednisone of 0.5-1.0mg/kg for 4-6 weeks.[16]

Rosacea has been shown to respond in doses of 0.5-1.0mg/kg/day in the past, however, more recent studies showed good efficacy in doses as low as 10mg/day.[17]

Potential Side-Effects of Isotretinoin Therapy

Oral isotretinoin produces predictable manageable side-effects that are, for the most part, reversible on discontinuation of therapy. Most are similar to those seen in high dose vitamin A therapy and are mucocutaneous in nature.[5] These include dry cracked lips, xerosis of the skin, mucous membranes and eyes. Musculoskeletal symptoms such as myalgia and arthralgia tend to be transient and dose related to exercise. Skin fragility has been reported and skin surgery should be avoided for 4-6 months. Wax epilation is also not desirable in this timeframe due to risk of skin fragility and dermatitis.[5] (See Table 2.)

Elevated levels of lipids and liver enzymes have been associated with therapy, though 20 years of clinical experience shows them to be of little clinical significance. A recent pharmacogenetic study concluded that "people who develop hypertriglyceridemia during isotretinoin therapy, as well as their parents, are at increased risk for future hyperlipidemia and the metabolic syndrome."[18] Therefore the physician may take advantage of this side-effect to predict the risk of the patient and their first degree relatives of developing diabetes, high blood pressure and obesity later in life. A full pre-treatment CBC and differential, fasting triglyceride (TG), alanine aminotransferase (ALT) and, in females, beta human chorionic gonatotropin (hCG) in serum or urine are recommended for baseline and should be repeated 4 weeks later. Abnormal results should

Dosage	Concomitant systemic disease
Standard Regimen	Diabetes mellitus, epilepsy, spina bifida, ulcerative colitis and Crohn's (if significant malabsorption may require higher cumulative dose)
0.25-0.5mg/kg/day. Increase at 2 month intervals to 0.5, and then 1.0mg/kg/day (24 week total)	Chronic renal failure, hypertriglyceridemia, immunosuppression, manic-depressive psychosis, myalgic encephalopathy, motor neuron disease, multiple sclerosis, renal dialysis, renal or cardiac transplant
Initial 20mg/week, increase by 20mg/week x 7 weeks until 20mg, b.i.d.	Behçet's Syndrome, idiopathic thrombocytopenic purpura, leukemia, mitochondrial degeneration, paroxysmal nocturnal hemoglobinuria, polymyalgia rheumatica, cerebellar spongiform encephalopathy

Table 1: Appropriate isotretinoin dose for concomitant systemic disease.[12]

Adverse Effect	Incidence	Comments
Teratogenicity		Isotretinoin is contraindicated during pregnancy.
Mucocutaneous • Dry Lips	96%	Apply lip salve or petrolatum.
• Facial Dermatitis	55%	Apply non-comedogenic moisturizer.
• Dry nose	51%	Apply nasal lubricant. Epistaxis usually mild.
• Dry skin, pruritus, desquamation, irritant dermatitis	20-50%	Pruritus usually secondary to dry skin; peeling of palms and soles; eczematous changes: moisturize or apply hydrocortisone 1% ointment
• Conjunctivitis	19%	More common in contact lens users. Use artificial tears.
• Hair loss	13%	Dose related and usually reversible. If severe, decrease or stop treatment. Persistent in 0.5% of patients treated.
• Impetiginization	7.5%	Staphylococcal impetiginization should be suspected when severe cheilitis, nasal vestibulitis, dermatitis develops. Treat with topical or oral antibiotics.
• Photosensitivity	1-5%	Minimize sun exposure; majority of patients have no trouble taking isotretinoin during summer.
Arthralgia and Myalgia	15-20%	Usually transient or episodic and dose related to exercise; nonsteroidal anti-inflammatory agents are rarely required.
Headache	5-16%	Usually mild and requires no treatment. If severe and associated with impaired concentration and blurred vision, check for pseudotumor cerebri (0.5% incidence). Stop and restart at a lower dose when better. Avoid concurrent use of Tetracycline.
Depression/Mood swing	Uncommon	Caution is required in patients with a history of severe depression. Patients should be monitored for mood changes during therapy.
Ophthalmic • Impaired night vision	Unknown	Rarely persists. Warn patients to be careful when driving at night.

Table 2: Side-effects of isotretinoin and their management. (Adopted from Miller.[19])

be repeated as well, as should dosage increases. Monthly pregnancy testing should continue until 1 month after cessation of therapy without exception. Recommendations apply to otherwise healthy individuals and those with prior histories of hyperlipidemias, blood sugar or liver abnormalities may require increased testing frequencies. (See Table 3.)

The Depression Controversy

Isotretinoin has been the subject of negative media coverage. It has been linked with mood alteration and increased suicide risk. Certainly, the high profile incident of the unfortunate suicide of the son of a US Congressman while taking the drug did promote controversy. There have been a number of recent retrospective studies into this possible link and none have been able to support its existence.[20-23] A retrospective data analysis by Jick, et al, of 20,895 acne patients,[21] almost one-third of whom had been on isotretinoin, found the estimated relative risk of acne patients for depression and suicidal behavior approximately equal in the oral antibiotic and isotretinoin groups.

In an exhaustive review of the existing literature and MedWatch reports, Jacobs, et al, concluded that there was no evidence to support a causal connection of the drug to depression or suicide, with the reported cases not meeting the established criteria for causality.[20] Neither could they establish a molecular mechanism linking the two. Adverse Drug Reaction reports made the regulatory authorities worldwide (1982-2000) suggest that depression and suicide or suicide attempt rates are well below those of the general population from CDC data. (See Table 4.) As their skin improves, isotretinoin patients' moods also tend to improve, rather than the opposite.[22] To date, no causal relationship between isotretinoin and psychiatric adverse events has been established. Hopefully, ongoing prospective studies will clarify this further.

Lab Test	Testing Frequency	Possible Effect	Cirteria for Intervention	Incidence of Effect	Recommended Action
Complete Blood Count Differential	Baseline and at 4 weeks	Neutropenia Thrombocytopenia	<1,000/ml <50,000/ml	Uncommon asymptomatic self-limiting	Reduce dose by 50% Repeat test in 4 weeks
Fasting Triglyceride (TG)	Baseline and at 4 weeks	Hypertriglyceridemia Pancreatitis	>8mmol/l or increase of 5mmol/l from baseline	25%	Stop drug. Repeat test in 2 weeks. Restart at 50% dose. Low fat diet.
Alanine Aminotransferase (ALT)	Baseline and at 4 weeks	Increased ALT Hepatocellular injury	3 x upper limit of normal	15%	Repeat after 4 weeks. Review medication history.
B-hCG (Serum/urine)	Baseline, then monthly	Pregnancy detection	Positive test	N/A	Stop drug. Repeat test. Counsel patient.
Blood sugar (known or suspected diabetes	Varies with degree of abnormality	Hyperglycemia	Uncontrolled hyperglycemia	N/A	Closer monitoring ± Diet ± Medication

Table 3: Recommended lab monitoring on isotretinoin therapy.[5]

	Depression	Suicide/Suicide Attempt
Isotretinoin use (1982-2000) MedWatch	10-13/100,000 patients	1-17/100,000 patients
USA General Population (1980-92) CDC, aged 15-24 years	20,000/100,000 patients	20/100,000 patients

Table 4: Isotretinoin and psychiatric events.

Expectations of Therapy – Cure?

It has long been recognized that long-term/permanent, treatment-free remissions in patients with acne can most often be achieved with isotretinoin therapy. White, et al reported a long-term remission rate of 39% after one standard course of 1mg/kg in 179 patients at 3 year follow-up.[2] Recurrences required further isotretinoin in 19%, topical therapy in 17%, and oral antibiotics in 25%. A longer term 10-year study in 88 patients by Layton, et al yielded a 40% "cure" rate with further topical therapy, oral antibiotics, and isotretinoin required in 21%, 16% and 23% respectively.[1] Data analysis in both studies showed patients that received total cumulative doses >100mg/kg and 120mg/kg had significantly better response than those on lower doses.

Treatment Failures

Non-responding patients to "normal" courses of isotretinoin may have been responders had the following potential pit-falls been adequately addressed during the initial course in assessing response:

- Compliance: check the lips for signs of cheilitis.
- Isotretinoin must be taken with a fat containing food.
- Insufficient dosage: clinical experience has shown that the dosing guidelines given in the product monograph are inadequate to achieve optimal response in most patients.
- Truncal acne, family history, early onset before age 12, long established acne that has been inadequately treated for years: all require more aggressive treatment.
- Ovarian cause (PCOS) may require hormonal therapy.

Costs in Perspective

It has been determined that long-term therapy in the management of moderate-to-severe acne with rotational oral antibiotics, hormonal and topical therapies have been shown to be less cost-effective than isotretinoin.[24-26]

Conclusion

Since the introduction of isotretinoin for acne therapy, the usage guidelines for the drug have widened considerably.[3-5] Initially, two or three failed courses of adequately dosed oral antibiotics would occasion its use. Now with the known efficacy of isotretinoin, its proven pharmacoeconomic advantage, the realization that even superficial acne can permanently scar, and the psychosocial impact of acne on patients of all ages, it has become the standard of care for not only scarring, but also selected indication-guided cases of non-scarring acne.

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Anticoagulants and Blood Thinners During Cutaneous Surgery: Always, Sometimes or Never?

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ABSTRACT

There is no consensus with regard to perioperative blood thinner management in patients undergoing cutaneous procedures. The rationale and problems associated with blood thinners during cutaneous surgery are examined and the preoperative screening and surgical management of patients taking anticoagulant medicines discussed. There are many studies that support continuation of blood thinners during cutaneous procedures supporting the conclusion that blood thinners should not be discontinued for cutaneous procedures.

KEY WORDS: *blood thinners, cutaneous surgery*

Anticoagulant medicines are used to treat individuals at risk for primary or recurrent thromboembolism. During major procedures, such as intraabdominal, intracranial, orthopedic or cardiothoracic, blood thinning agents are usually discontinued or at least modified in an attempt to prevent undue intraoperative and postoperative bleeding. Subsequent to such procedures, blood thinners are reintroduced to treat the underlying thromboembolic disorder. This process of manipulating the level of anticoagulation can be time consuming, requires multiple blood tests and exposes patients to increased risk of thromboembolism, hemorrhage or both.

Patients at risk for thromboembolic events include those with mechanical heart valve(s), valvular heart disease, underlying coagulopathy, atrial fibrillation, history of stroke, pulmonary embolism, myocardial infarction, or deep venous thrombosis. Commonly prescribed anticoagulant medicines include antithrombin agents such as warfarin or heparin products, and antiplatelet agents such as aspirin, thienopyridines or glycoprotein IIb/IIIa inhibitors (Table 1). Patients at risk for thromboembolism typically take one or more of the aforementioned anticoagulants under the guidance of the primary care provider.

Historically, dermatologic surgeons have implemented general surgery practice guidelines in managing blood thinning medicines prior to and during cutaneous procedures. Based on advice given for previous surgery, some patients undergoing cutaneous surgery stop anticoagulation medicines themselves without consulting a physician. Other patients stop anticoagulant medicines on the advice of their referring physician, surgeon or both. Frequently patients on long-term anticoagulation arrive for their cutaneous procedures without the protection afforded by their vital blood thinning medicines.

Thromboenbolic events have been reported in cutaneous procedure patients whose anticoagulants were stopped in order to limit ostensible perioperative bleeding.[2] A recent survey of 168 Mohs micrographic surgeons reported 46 patients who experienced thromboembolic events, including three deaths and 24 strokes after brief perioperative blood thinner cessation.[3] Fifty-four percent of the thromboembolic events occurred after warfarin was discontinued and 39% had thromboembolism after aspirin was withheld.[3] Discontinuation of newer blood thinners such as ticlopidine, clopidogrel and ardeparin has also been associated with thromboembolism.[1]

A retrospective study of 653 patients undergoing cutaneous procedures was performed by Otley, et al in 1996. Some of the patients had their blood thinners (antiplatelet agent or warfarin) discontinued preoperatively. The risk of severe intraoperative and postoperative bleeding in patients taking blood thinners was found very low, not significantly reduced by preoperative blood thinner discontinuation.[4] Several recent studies have documented that cutaneous procedure patients taking aspirin have no significant risk of postoperative hemorrhagic complications.[5-7] Others have reported no significant risk of postoperative hemorrhage in cutaneous surgery patients taking therapeutic doses of warfarin.[8,9] Furthermore, successful procedures in patients taking therapeutic levels of warfarin without undue postoperative bleeding have been documented in many surgical subspecialties, including cardiothoracic, gastrointestinal, urology, oromaxillofacial, vascular, and ophthalmology.

Cutaneous surgeons may cite anecdotal experience as grounds for blood thinner discontinuation. Some surgeons believe blood thinners cause undue intraoperative bleeding, which interferes with operative dissection. Perceiving undue intraoperative bleeding, the surgeon may inquire as to whether the patient has recently taken blood-thinning medicines. A recent study by West, et al showed that cutaneous surgeons are unable to accurately predict blood thinner status of the patient based on intraoperative oozing.[10] This study helped to dispel some of the myths associated with blood thinners in the setting of cutaneous surgery.

I do not advise my patients undergoing cutaneous procedures to discontinue any blood thinner used to treat a thromboembolic disorder. The following techniques may prove helpful in screening and treating cutaneous surgery patients, many of whom take one or multiple blood thinning medicines.

Class	Subclass	Compound/Trade name
Antiplatelet agents	Aspirin	------
	ADP induced platelet activation inhibitors	Clopidogrel (Plavix®) Ticlopidine (Ticlid®)
	Platelet glycoprotein IIb/IIIa antagonists	Abciximab (Reopro®) Eptifibatide (Integrilin®) Tirofiban (Aggrastat®)
Antithrombin agents	Unfractionated heparin	------
	Direct thrombin inhibitors	Bivalirudin (Angiomax™) Hirudin (Refludan®) Argatroban (Novastan®)
	Low molecular weight heparin	Enoxaparin (Lovenox®) Dalteparin (Fragmin®) Ardeparin (Normiflo®) Danaparoid (Orgaran®) Tinzaparin (Innohep®)
	Coumarin	Warfarin (Coumadin®)
	Factor Xa inhibitor	Fondaparinux (Arixtra®)
Thrombolytic agents	Plasminogen activators	Streptokinase (Streptase®) Alteplase (Activase®) Reteplase (Retavase®) Tenecteplase (TNKase®)

Table 1: Antithrombotic agents approved in the U.S. Modified from Alam M, Goldberg LH.[1]

Preoperative Screening

1. Ask patient about bleeding complications from past procedures (dental extraction, teeth cleaning, invasive surgery). Inquire if they have experienced spontaneous bleeding (GI bleeding, epistaxis) or a large hematoma after relatively minor trauma. Does the patient bleed for a prolonged period after minor cuts and scratches?

2. Routine preoperative INR, bleeding time, and prothrombin (PT) are not usually helpful in predicting operative and postoperative bleeding. Determine if patient has had erratic International Normalized Ratio (INR) values in the past. If values are supratherapeutic (INR>5), the risk of postoperative bleeding increases significantly.

3. Inquire about other conditions that may contribute to bleeding: alcoholism, liver disease, inheritable coagulopathies (hemophilia, Von Willebrand's disease), acne rosacea, and the use of other anticoagulants that could potentiate bleeding such as vitamin E, Ginko biloba, and nonsteroidal anti-inflammatory drugs.

4. Some patients take empiric aspirin and have no obvious underlying risk of thromboembolism. Many of these patients take aspirin at the advice of friends, family or primary care provider. It is reasonable to temporarily stop such empiric aspirin intake.

5. If patient has a history of severe postoperative bleeding complications, consider non-surgical modalities such as radiation.

Operative Techniques

1. Meticulous homeostasis is vital in managing cutaneous surgery patients taking blood thinners. Make sure to have excellent lighting and wound retraction to assist isolating arteriole bleeding. Use a hemostat to grasp and close the vessel. Secure vessel closed with absorbable ligature. Employ electrocoagulation. If automatic implantable cardioverter defibrillator (AICD) or pacemaker is present, use bipolar forceps to stop small vessel bleeding.

2. Simplify wound reconstruction. Discuss simplifying the reconstruction with the patient. Review the risks of a more noticeable scar vis-à-vis the need for continued anticoagulation. A flap, which may mobilize large amounts of skin, is probably at greater risk for hematoma and wound necrosis. Pursestring closures may work well to minimize postoperative hemorrhage. A purse-string closure does not require undermining and serves to tamponade peripheral wound bleeding. The center of the wound remains open and acts as a drain.

3. Limit subcutaneous undermining. In severe cases, when patients have repeatedly soaked through the dressing whilst in the waiting room, I have closed wounds primarily without any undermining, limiting potential bleeding foci. Close the wound meticulously with multiple layers of absorbable suture to minimize dead space.

4. Second intention healing is also a reasonable choice for wound management. In addition, one may apply Gelfoam® to the wound and secure a pressure dressing over the Gelfoam®. In severe cases, the

surgeon can also run absorbable suture such as 5-0 Monocryl®, continuously around the wound edges.

5. Fenestrated full thickness skin grafts with a tie-over bolster provide wound tamponade and a collagen substrate for hemostasis.

6. During wound repair, consider using local anesthesia without a vasoconstrictor, such as epinephrine. Vasoconstrictors provide helpful operative bleeding reduction, prolong anethesia duration and reduce total anethetic dose. However, reactive vasodilatation in the postoperative period may predispose to hematoma because potential bleeding points, such as arterial bleeding, are not recognized at surgery.[11]

7. Drains: in cases where refractory bleeding may continue as a generalized slow oozing, often seen in underlying coagulopathies, I will place a Jackson-Pratt or Penrose drain into the wound prior to repair and withdraw the drain after 48 hours.

8. Prescribe analgesics. This not only keeps the postoperative period more restful but also reduces anxiety, pain and elevated blood pressure. High blood pressure increases intraoperative and postoperative bleeding.

9. Place the wound at rest. Have patient avoid stooping, bending or lifting anything heavier than a 12oz. soda for 72 hours. Have them elevate the site and keep the area dry. Avoid any strenuous activity for 1 week. Emphasize that NSAIDs and aspirin are not to be taken for pain. Give written instructions.

Conclusion

Evidence continues to mount favoring blood thinner maintenance during cutaneous surgery. The risk of life-threatening thromboembolism associated with even brief cessation of blood thinners is significant. Unfortunately, primary care providers will remain unaware of the bleeding risks associated with cutaneous procedures such as Mohs excision and wound repair. The cutaneous surgeon should be aware of the various techniques and tools to reduce the risk of intraoperative and postoperative bleeding in patients taking blood thinners. Notwithstanding, bleeding complications carry far less morbidity and mortality than that of thromboembolism.

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Update on Drugs

Class	Name/Company	Approval Dates and Comments
Corticosteroid	**Clobetasol Propionate Foam** *Luxiq*® Connetics	The US FDA approved this super-potent corticosteroid foam in December 2003, for the short-term topical treatment of inflammatory and pruritic manifestations of corticosteroid-responsive scalp dermatoses.
Cosmetic Treatment	**Hyaluronic Acid** *Restylane*® Medicis	The US FDA approved this dermal filler in December 2003, for the correction of moderate-to-severe facial wrinkles and folds. Restylane® is a dermal filler made of a biodegradable non-animal stabilized hyaluronic acid (NASHA™).
Oncologic Agent	**Oblimersen Sodium** *Genasense*™ Aventis/Genta	The US FDA received a New Drug Application in December 2003 for use of this product in combination with dacarbazine for the treatment of patients with advanced malignant melanoma. The application was submitted under the Fast Track program.
Oncologic Agent	**Metvix** Photo Cure/Galderma	Switzerland's regulatory agency approved this novel skin cancer treatment in November 2003, for the treatment of actinic keratosis and basal cell carcinoma. Metvix combines the local application of a cream that is selectively absorbed into the cancer cells then illuminated with a proprietary red light source (Aktilite®) to activate the drug. It is now approved for marketing and sales in 16 European countries, in addition to New Zealand and Australia.

Drug News

Antibacterial Agent	Cubist Pharmaceuticals and Chiron Corporation announced in October 2003, a license agreement for the development and commercialization of Cubist's antibiotic Cubicin® (daptomycin for injection) in Western and Eastern Europe, Australia, New Zealand, India and certain Central American and Middle Eastern countries. The US FDA recently approved this antibiotic for the treatment of complicated skin and skin structure infections caused by Gram-positive bacteria.
Anti-acne Agent	Micrologix Biotech reported in November 2003, that a Phase IIb study of their antimicrobial cationic peptide MBI 594AN achieved statistically and clinically significant efficacy. In this study, 225 patients were treated twice daily with one of two dose levels (2.5% and 1.25%) of this product or with the vehicle, and acne lesion count reductions at various time points were evaluated. The 2.5% dose achieved statistically significant superiority at 6 weeks in reducing all three lesion parameters measured: inflammatory lesions, non-inflammatory lesions and total lesions.
Antifungal Agent	Schering-Plough reported in October 2003, that Noxafil® (posaconazole oral suspension) was effective in treating coccidioidomycosis, a potentially deadly fungal disease, after standard antifungal therapies have failed. Six patients with coccidioidomycosis received oral Noxafil® and all six initially received benefit from the drug, while five were long-term successes during the follow-up period.
Wound Care	Effective January 1, 2004, the Ross Products Division of Abbott Laboratories will assume US sales and distribution responsibility for Collagenase Santyl® Ointment. Available by prescription, this ointment is indicated for debridement of chronic dermal ulcers and severely burned areas.

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