ABSTRACT

Disorders of hyperpigmentation are difficult to treat, particularly in dark-skinned individuals. The goal is to reduce the hyperpigmentation without causing undesirable hypopigmentation or irritation in the surrounding normally pigmented skin. The psychosocial impact caused by these disorders must be considered. Although there are many effective therapeutic modalities available, there are potentially significant side-effects associated with treatment. The most commonly used treatment is topical hydroquinone. There are other phenolic agents, such as N-acetyl-4-cystaminylphenol (NCAP), that are currently being studied and developed. The non-phenolic agents, which include tretinoin, adapalene, topical corticosteroids, azelaic acid, arbutin, kojic acid, and licorice extract, are also used for hyperpigmentation disorders.

Key Words: hyperpigmentation, management

Hydroquinone and related compounds reduce the production of melanin by their inhibition of the enzyme tyrosinase. Topical corticosteroids also inhibit tyrosinase activity and affect endoplasmic reticulum secretory function of melanocytes. Agents such as salicylic acid and glycolic acid act to remove melanin in the epidermis by their peeling action. Tretinoin, which has a mild peeling effect, acts in a similar manner. It may also inhibit tyrosinase.

Hydroquinone

Hydroquinone, which is a hydroxyphenolic chemical, has been the gold standard for treatment of hyperpigmentation for over 50 years. It acts by inhibiting the enzyme tyrosinase, thereby reducing the conversion of DOPA to melanin. Some of the other possible mechanisms of action are the destruction of melanocytes, degradation of melanosomes, and the inhibition of the synthesis of DNA and RNA.1
Hydroquinone can be compounded into 5%-10% concentrations, but at these strengths, may be irritating and unstable. The 2% concentrations of hydroquinone available over the counter in the US and Canada are not as efficacious as the 3% and 4% prescription formulations, as their onset of action is later than with the higher concentrations. Antioxidants, such as vitamin C and retinoids, as well as alpha-hydroxy acids may be used as additives to increase penetration and enhance efficacy. Exogenous ochronosis with the use of hydroquinone has been reported in dark-skinned patients, in particular South African women who frequently use very high concentrations of hydroquinone over large surface areas. 2 Although hydroquinone is used extensively in North America, there have only been about 30 reported cases of exogenous ochronosis from hydroquinone use in North America.

Adverse reactions from hydroquinone use include irritant and allergic contact dermatitis, and nail discoloration. Postinflammatory hyperpigmentation may occur from the contact dermatitis. Hypopigmentation of the normal skin surrounding the treated areas may also occur. These usually resolve with the discontinuation of the hydroquinone treatment. 2

Other Phenolic Agents

Monobenzone, the monobenzyl ether of hydroquinone, is a special topical phenolic agent, which is indicated only for the final depigmentation of disfiguring vitiligo. It is applied topically to permanently depigment normal skin surrounding vitiliginous areas in patients with disseminated vitiligo (greater than 50% body surface area). The cream is applied in a thin layer, rubbed into the normally pigmented areas two or three times daily. Depigmentation is usually achieved after 6-12 months with 20% monobenzone treatment. It should then be applied only as often as required to maintain depigmentation. Monobenzone cream can produce satellite depigmentation at sites distant from the site of initial application.

N-acetyl-4-cysteaminy1phenol (NCAP) is another phenolic agent that is currently being developed and is not yet available in North America. NCAP acts to decrease intracellular glutathione by stimulating pheomelanin rather than eumelanin. 3 It also inhibits tyrosinase activity, has been found to be more stable, and causes less irritation than hydroquinone. In a retrospective study of 12 patients with melasma using 4% NCAP, 66% showed marked improvement, and 8% showed complete loss of melanoma lesions. Changes of melanoderma were evident after 2-4 weeks of daily topical application of NCAP. 3

Azelaic Acid

Azelaic acid is a naturally occurring non-phenolic, saturated, nine-carbon dicarboxylic acid. Its use originated from the finding that Pityrosporum species can oxidize unsaturated fatty acids to dicarboxylic acids, which competitively inhibit tyrosinase. Azelaic acid was initially developed as a topical drug with therapeutic effects for the treatment of acne. However, because of its effect on tyrosinase, it has also been used to treat melasma, lentigo maligna and other disorders of hyperpigmentation. 4 Azelaic acid has been reported to be effective for hypermelanosis caused by physical or photochemical agents, and lentigo maligna melanoma as well as other disorders characterized by abnormal proliferation of melanocytes. Its mechanism of action is to inhibit DNA synthesis and mitochondrial enzymes, thereby inducing direct cytotoxic effects toward the melanocyte. 4 Topical azelaic acid has no depigmentation effect on normally pigmented skin, freckles, senile lentigines, and nevi. This specificity may be attributed to its selective effects on abnormal melanocytes.

Azelaic acid can be used for postinflammatory hyperpigmentation in acne. 7 Free radicals are believed to contribute to hyperpigmentation, and azelaic acid acts by reducing free radical production. 4 Azelaic acid 20% is currently available in the US and is only indicated for the treatment of acne, although it has off-label use for hyperpigmentation. In the treatment of melasma, a 24-week study in South America found that a 20% concentration of azelaic acid was equivalent to 2% hydroquinone. 9 In the Philippines, a study found that 20% azelaic acid was better than 2% hydroquinone. 10

Kojic Acid

Kojic acid (5-hydroxy-2-(hydroxy methyl)-4-pyrone), a naturally occurring hydrophilic fungal derivative evolved from certain species of Acetobacter, Aspergillus and Penicillium, is used in the treatment of hyperpigmentation disorders. 10 It acts by inhibiting the production of free tyrosinase with efficacy similar to hydroquinone. In Japan, kojic acid has been increasingly used in skin care products. This is because, until recently, topically applied kojic acid at 1% concentration had not exhibited any sensitizing activity. 11 However, more recent long-term Japanese studies have shown that kojic acid has the potential for causing contact dermatitis and erythema. 12

Arbutin

Arbutin, which is the b-D-glucopyranoside derivative of hydroquinone, is a naturally occurring plant derived compound that has been used for postinflammatory hyperpigmentation. 13 It is effective in the treatment of disorders of hyperpigmentation characterized by hyperactive melanocytes. 14 The action of arbutin is dependent on its concentration. Higher concentrations are more efficacious than lower concentrations, but they may also result in a paradoxical hyperpigmentation. 11 In comparative in vitro studies of various compounds used to improve the appearance of disorders of hyperpigmentation, arbutin was found to be less toxic than hydroquinone. A dose-dependent reduction in tyrosinase activity, as well as melanin content in melanocytes, was also demonstrated. 14

Licorice Extract

Licorice extract is not yet available in North America, but has been used in other parts of the world, particularly in Egypt. Its mechanism of action is similar to that of kojic acid. The main component of the hydrophobic fraction of licorice extract is glabridin, which has an effect on the skin. Studies investigating the inhibitory effects of glabridin on melanogenesis and...
inflammation have shown that it inhibits tyrosinase activity of melanocytes. No effect on DNA synthesis was detectable.15

**Topical Retinoids**

The efficacy of topical tretinoin 0.05-0.1% as monotherapy for postinflammatory hyperpigmentation has been reported.16 Tretinoin was also used as monotherapy in a study on 38 African-American patients with melasma and 68%-73% of patients improved. In 88% of the patients, moderate side-effects of desquamation and erythema were observed.17,18 Darker skinned patients who develop a dermatitis from tretinoin may develop postinflammatory hyperpigmentation secondary to the dermatitis. The mechanism of action of tretinoin in the treatment of melasma is poorly understood. Clinical improvement has been found to be associated with a reduction in epidermal melanin, possibly as a result of the inhibition of tyrosinase by the action of tretinoin.19

Although tretinoin can be effective as monotherapy for hyperpigmentation and melasma, it requires 20 to 40-week treatment periods. Tretinoin can also be used in conjunction with hydroquinone or other depigmenting agents to improve efficacy. The first published study of combination therapy used tretinoin 0.1%, hydroquinone 5%, and dexamethasone 0.1% for postinflammatory hyperpigmentation.20 Tretinoin was shown to reduce the atrophy of the corticosteroid and facilitated the epidermal penetration of the hydroquinone. The tretinoin-induced irritation was reduced by the corticosteroid. The first triple combination topical therapy approved by the US FDA for melasma is a modified formulation comprising fluocinolone acetonide, hydroquinone 4% and tretinoin 0.05%. In studies of patients with melasma, 78% had complete or near clearing after 8 weeks of therapy. Similar results and favorable safety profile were seen in a 12-month study.21 In a randomized clinical trial, the efficacy of adapalene 0.1% was found to be comparable to that of tretinoin 0.05% cream in the treatment of melasma (mainly epidermal type). The results showed fewer side-effects and greater acceptability among patients using adapalene.22

**Conclusion**

The treatment of hyperpigmentation disorders can be a long process. The psychosocial impact of these disorders should be taken into consideration. There are several topical treatment options available, the most common of which is hydroquinone. The use of combination therapy and monotherapy with non-phenolic agents is increasingly common. These treatment options are primarily for epidermal disorders of hyperpigmentation. Dermal disorders of hyperpigmentation are difficult to treat, and have not been effectively managed using currently available therapy.

**References**


Ciclopirox Shampoo for Treating Seborrheic Dermatitis

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3University of Western Ontario, London, Ontario, Canada

Clinically, seborrheic dermatitis presents as red, flaking, slightly greasy-looking patches, which are located primarily on the scalp, nasolabial folds, ears, eyebrows and chest. The degree of flaking and erythema can vary markedly between patients.1 The exact cause of seborrheic dermatitis is not known, however, a number of predisposing factors have been reported. Such endogenous host factors include nutritional,2 environmental,3,4 and immunological5 factors, as well as the presence of Malassezia yeast.6

While there is some controversy with regard to the relationship between seborrheic dermatitis of the scalp and dandruff, it has been argued that dandruff is a mild form of seborrheic dermatitis.7,8 Furthermore, the relationship between Malassezia yeasts and the effective treatment of seborrheic dermatitis with antifungal agents helps to support the claim that these yeasts are the primary cause of seborrheic dermatitis.9

Due to the fact that there is an increased prevalence of seborrheic dermatitis in HIV-positive and AIDS patients,10,11 it is thought that the disease may be caused by an abnormal immune response to Malassezia. However, it is unclear exactly what this immune response might be. Many individuals without seborrheic dermatitis have antibodies to Malassezia yeasts and while some authors have found that the level of IgG antibodies to the yeasts is increased in patients with seborrheic dermatitis,12 others have found no difference in the number of antibodies produced by patients with seborrheic dermatitis and controls.

It has recently been suggested that the reaction by seborrheic dermatitis patients to Malassezia is best characterized as an irritant response involving an inflammatory reaction and that reduction of Malassezia yeast on the skin reduces the clinical signs of seborrheic dermatitis.

Ciclopirox

Ciclopirox is the ethanolamine salt of 6-cyclohexyl-1-hydroxy-4-methyl-2(1H)-pyridone.16 The empirical formula of ciclopirox is C12H17NO2, with a molecular weight of 207.27. Ciclopirox shampoo 1% is a colorless, translucent solution,17 which has been used in the treatment of seborrheic dermatitis.

In addition to its effect on Malassezia yeasts, ciclopirox has been shown to decrease inflammation. Rosen et al.18 found that the anti-inflammatory activity of ciclopirox was greater than that of several azole agents or hydrocortisone. Ciclopirox appears to exert its anti-inflammatory effect via several pathways, including the inhibition of 5-lipoxygenase and cyclo-oxygenase.19,20

Clinical Trials of Ciclopirox

Vardy et al.21 conducted a double-blind, randomized, placebo-controlled clinical study of ciclopirox olamine 1% shampoo to determine its effectiveness in the treatment of scalp seborrheic dermatitis. One hundred and two patients were randomly selected to apply either ciclopirox olamine 1% shampoo or the vehicle shampoo to the scalp for 5 minutes,
twice per week for 4 weeks. Signs and symptoms of erythema, scaling, and pruritus were assessed at the end of the study, which revealed that 93% of the ciclopirox shampoo-treated patients had significantly improved or cleared compared to 41% in the placebo group (P=0.00001). Another double-blind, randomized, vehicle-controlled study was conducted to assess the efficacy of 1% ciclopirox shampoo in the treatment of seborrheic dermatitis of the scalp. Subjects were randomly selected to 5ml (10ml for shoulder-length hair or longer) of either 1% ciclopirox or vehicle shampoo twice per week for 4 weeks. Grading of erythema, scaling, and the overall status of seborrheic dermatitis was performed at week 4, using a 6-point rating scale (0=none, 1=slight, 2=mild, 3=moderate, 4=pronounced, and 5=severe). Effective treatment was defined as a score of 0 (or 1 if baseline score was ≥3) for the combined rating of global status, erythema, and scaling. It was reported that 26% of the ciclopirox-treated patients were effectively treated compared to 13% of the vehicle group (P=0.0001).

Adverse Effects
Ciclopirox shampoo 1% was used twice a week in 626 patients. Increased itching was the most frequent adverse event found in 1% of the subject population. Furthermore, application reactions, such as burning, erythema, and itching also occurred in 1% of the subjects.

Dosage and Administration
After wetting hair, apply approximately 1 teaspoon (5ml) of ciclopirox shampoo 1% to the scalp. If the patient has long hair, it is recommended to use up to 2 teaspoons (10ml). Lather and leave on for 3 minutes before rinsing. Treatment should be repeated twice per week for 4 weeks, with a minimum of 3 days between each application.

Conclusion
Evidence suggests that an abnormal or inflammatory immune system reaction to Malassezia yeasts may be the cause of seborrheic dermatitis. An available treatment for this disease is ciclopirox shampoo, which is an antifungal agent that also has antibacterial and anti-inflammatory properties. The proven efficacy and safety of ciclopirox shampoo in the treatment of seborrheic dermatitis of the scalp makes it an important addition to the treatment options available.

References
An appreciation of the concept of the superficial musculoaponeurotic system (SMAS) occurred in the 1970s. SMAS manipulation is a common approach to face-lifting, and appropriate modification of the SMAS can produce long lasting esthetically pleasing results. SMAS rhytidectomy begins with the creation of a cheek skin flap. The SMAS is handled in a number of ways. The simplest approach is to plicate the SMAS. The plication approach relies upon folding the SMAS onto itself without SMAS undermining. This technique tends to be a very safe approach to face-lifting as the SMAS and sub-SMAS structures are left intact.

Baker popularized the lateral SMASectomy approach. His method, similar to plication, does not undermine the SMAS. The plication approach relies upon folding the SMAS onto itself without SMAS undermining. This technique tends to be a very safe approach to face-lifting as the SMAS and sub-SMAS structures are left intact. Baker's technique is also very safe as the facial nerve is protected by the parotid gland in the area of SMAS resection. More extensive SMAS management is obtained by creating a limited SMAS flap (conventional SMAS face-lift) or an extended SMAS flap. The SMAS flap is created in addition to the skin flap, and is separately repositioned.

While SMAS modification remedies many of the problems with the skin-only rhytidectomy, some surgeons felt that key elements of the aging face were inadequately corrected. Concern with the ability to adequately reposition the nasolabial fold and elevate the midface led to further surgical modifications. Techniques to reposition deeper tissues were developed, and this process culminated in the composite rhytidectomy. In the late 1960s, Skoog described a sub-platysmal plane of dissection that left the skin and platysma together as a single unit. Skoog’s initial work...
prompted surgeons to create deeper planes of dissection. The deeper tissues were left attached to the overlying skin and repositioned as a single unit. In the early 1990s, Hamra described the composite rhytidectomy. This technique involves creating a deep plane of dissection for tissue suspension. A unified flap that consists of skin, platysma, midface cheek fat and orbicularis is created, elevated, and repositioned. This approach seeks to add, among other things, cheek fat and nasolabial fold correction into the face-lift procedure.5 Concern has been expressed with regard to the relatively long recovery period from these deep plane dissections.3 Figure 1 illustrates the planes of dissection in the traditional face-lift techniques discussed, while Table 1 summarizes various rhytidectomy approaches.

As face-lift approaches multiplied and became more complex, patient desires changed. Younger patients began to seek cosmetic surgery and trends toward less invasive approaches to facial rejuvenation developed. Patients wanted less downtime from their procedure. Additionally, despite increased tissue rearrangement with more complex surgery, a clear and compelling benefit of one type of face-lift over another failed to materialize. While controversial, the few studies that directly compared the various techniques failed to show a significant difference in outcome.3,6 The desire for a less invasive face-lift prompted techniques such as Saylan’s “S-lift” and Tonnard’s “Minimal Access Cranial Suspension” face-lift. These approaches rely upon a limited face-lift incision, conservative skin flap creation, and the use of sutures in a loop configuration to plicate the deeper tissues. No SMAS flap is created. Local anesthesia (with or without oral or IV sedation) is all that is required for these ambulatory, and in many cases office-based, procedures.7,8 In many cases, these limited approaches are augmented by the use of adjuvant procedures such as botulinum toxin injections, laser skin resurfacing or chemical peeling, fat transplantation, and soft tissue fillers to achieve the desired result through multiple small interventions rather than one more involved

<table>
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<tr>
<th>Face-Lift Technique</th>
<th>Essential Features</th>
<th>Comments</th>
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<tbody>
<tr>
<td>Skin Only</td>
<td>Skin flap created. No manipulation of deeper tissues.</td>
<td>Limited benefit.</td>
</tr>
<tr>
<td>SMAS Plication</td>
<td>Skin flap created. SMAS is folded on itself. No SMAS undermining.</td>
<td>Straightforward, limited anesthetic requirements.</td>
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<tr>
<td>S-Lift and Variants</td>
<td>Skin flap created. SMAS is plicated with purse string type sutures. No SMAS undermining.</td>
<td>Similar to SMAS plication with sutures elevating the SMAS and platysma. Limited anesthetic requirements.</td>
</tr>
<tr>
<td>Lateral SMASectomy</td>
<td>Skin flap created. SMAS overlying parotid is resected and tightened. No SMAS undermining.</td>
<td>Little risk of nerve injury. Limited recovery time.</td>
</tr>
<tr>
<td>SMAS Lift (conventional)</td>
<td>Skin flap created. Separate SMAS flap created. Flaps advanced independently.</td>
<td>Increased risk of nerve injury. Benefit over plication alone is uncertain.</td>
</tr>
<tr>
<td>SMAS Lift (extended)</td>
<td>Skin flap created. Separate SMAS flap created. Flaps advanced independently.</td>
<td>Similar to conventional SMAS lift with greater degree of SMAS flap undermining.</td>
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Table 1: Summary of rhytidectomy approaches.
procedure. Figure 2 shows a patient before a Minimal Access Cranial Suspension face-lift and at 1-year follow up.

These less invasive approaches have been favored by dermatologic surgeons. The popularity of these procedures stems from several factors. The procedure is performed on an outpatient basis, utilizing tumescent anesthesia and occasionally with moderate oral, IM, or IV sedation. Recovery from these procedures is relatively rapid and can be seen in a matter of a few days to weeks. Complications are few and minor. In Saylan’s original series, he noted that the most frequent complaint was short-term pain and tightness in the pre-tragal region. Temporary facial nerve palsy was observed in three secondary face-lift patients. The platysmal plicating suture caused temporary dimpling beneath the earlobe in most patients. In their series, Tonnard and colleagues also found this approach very safe. They noted that most patients returned to normal activity within one week. Both Saylan and Tonnard feel that their patients are achieving lasting benefit from this approach.

A number of face-lift alternatives and adjuvant procedures have been recently popularized. For the patient with primarily soft tissue ptosis and little skin redundancy, the use of percutaneously placed suspension sutures is an option. This approach has been proposed for elevation of the brow, midface, and jowl regions. The advantages of these procedures are the use of local anesthesia and minimal scarring, downtime and expense when compared with traditional surgical rhytidectomy. As no skin excision occurs, these techniques will not remove redundant skin and may be best suited for younger patients. Most surgeons using suspension techniques utilize a variety of nonabsorbable sutures. Recently, a

<table>
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<th>Technique</th>
<th>Essential Features</th>
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<tr>
<td>Radiofrequency energy (Thermage)</td>
<td>Contact cooling with no epidermal disruption. Seeks to achieve skin tightening.</td>
<td>New technology. Limited data to date. Simple to operate. Topical anesthetic only. No downtime.</td>
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<tr>
<td>Percutaneous Suspension Sutures (including APTOS)</td>
<td>Uses suture material to suspend ptotic soft tissues.</td>
<td>Does not address skin redundancy. Uncertain long-term correction. Local anesthetic only.</td>
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Table 2: Summary of the most promising minimally invasive facial rejuvenation techniques.
specially modified polypropylene suture with sharp, barb-like projections has been described. These percutaneously placed sutures, dubbed APTOS threads, serve to securely grasp and elevate soft tissues. Table 2 summarizes the most promising minimally invasive techniques.

**Conclusion**

While the myriad of options for face-lifting may seem confusing to physicians and patients at first glance, there are advantages and disadvantages to each. With more options available, we can cater our treatments for each patient. With proper education and a firm preoperative assessment of goals, the surgeon and patient can select the approach that optimizes their probability of a successful outcome. Clearly there is no one solution to all forms of facial aging.

**References**

## Update on Drugs

<table>
<thead>
<tr>
<th>Class</th>
<th>Name/Company</th>
<th>Approval Dates and Comments</th>
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<tbody>
<tr>
<td>Dermal Filler</td>
<td>Hylan-B gel</td>
<td>The US FDA approved this hyaluronic acid-based dermal filler in April 2004, for injection into the mid-deep dermis for correction of moderate-to-severe facial wrinkles and folds.</td>
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<td>Hylaform™</td>
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<td>Nabi Biopharmaceuticals</td>
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<td>Antipruritic Agent</td>
<td>Cetirizine HCl</td>
<td>The US FDA approved this new chewable formulation in March 2004, for the treatment of seasonal and perennial allergic rhinitis and chronic idiopathic urticaria in children ≥ 2 years of age.</td>
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<td>Zyrtec®</td>
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<td>Pfizer/UCB Pharma</td>
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<tr>
<td>HIV/AIDS</td>
<td>Injectable poly-L-lactic acid</td>
<td>A US FDA advisory committee unanimously recommended approval with conditions for this polymer in March 2004, for the correction of shape and contour deficiencies resulting from facial fat loss (lipoatrophy) in people with HIV. Conditions include a post-approval study, a physician training program, product use that is limited to people with HIV who have lipoatrophy, provision of product specification information and wording changes to the proposed label.</td>
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<td>SCULPTRA™</td>
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<td>Dermik</td>
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<tr>
<td>HIV/AIDS</td>
<td>Fosamprenavir</td>
<td>The European Committee for Proprietary Medicinal Products (CPMP) gave a positive opinion in March 2004, for this product for the treatment of HIV infection in adults in combination with other antiretroviral medications.</td>
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<td>Telzir®</td>
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<td>GlaxoSmithKline/Vertex Pharmaceuticals</td>
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<td>Antipsoriatic Agent</td>
<td>Genentech and XOMA announced preliminary results in March 2004, of a randomized placebo-controlled Phase II study with RAPTIVA® (efalizumab) in 107 patients with psoriatic arthritis. The study did not reach statistical significance at 12 weeks for the primary endpoint, ACR response, indicating that while psoriatic arthritis is associated with psoriasis, they are distinct diseases. This T-cell modulator was approved by the US FDA in October 2003, for the treatment of chronic moderate-to-severe plaque psoriasis in adults ≥ 18 years of age who are candidates for systemic therapy or phototherapy.</td>
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<tr>
<td>Antiviral Agent</td>
<td>A European Phase III trial of Polyphenon E Ointment achieved excellent results for the treatment of genital warts. The statistically significant trial with more than 500 patients showed a high and lasting efficacy of the drug with extremely low systemic adverse effects. US Phase III trials are ongoing with results expected by the end of 2004.</td>
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**Erratum:** There was an error in the Update on Drugs published in Volume 9, Issue 4 of the *Skin Therapy Letter*. Under Etanercept/Enbrel®, the company is listed as Wyeth Pharmaceuticals. It should be AMGEN Canada/Wyeth Pharmaceuticals (Canada) and Wyeth Pharmaceuticals (Europe).