

# Skin Therapy Letter<sup>®</sup>

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## New Developments in Topical Sequential Therapy for Psoriasis

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### ABSTRACT

*Topical agents for the treatment of psoriasis are indicated for patients whose affected area is <10% of their skin. However, for long-term use, their effectiveness can be limited. Topical sequential therapy involves the application of a class I corticosteroid and calcipotriene in three different phases: the clearance phase, the transition phase and the maintenance phase. It is an accepted and widely practiced technique that provides a balance between maximizing efficacy and minimizing side-effects thus offering patients rapid clearance of their psoriatic lesions and long-term maintenance of remission.*

**Key Words:** *topical treatment, psoriasis, sequential therapy, calcipotriene, corticosteroids*

Topical therapy is central in the treatment of psoriasis, and is indicated for most patients who have 20% or less of their body surface affected. Topical agents are associated with a lower side-effect burden compared with systemic therapies, which are generally reserved for patients with severe or non-responsive disease. However, individual topical agents have their own limitations. Topical corticosteroids, the most widely prescribed topical agents for psoriasis in the US, are highly effective in short-term use, but are associated with the potential for significant side-effects with long-term use, including atrophy, telangiectases, striae, and tachyphylaxis.

### *Sequential Therapy*

The technique of sequential therapy was developed to maximize the short-term efficacy of topical agents while minimizing side-effects associated with long-term maintenance therapy. Other topical agents, such as the vitamin D analog calcipotriene, are safer in long-term use, but they are also slower acting than commonly used high-potency topical steroids. Combining agents such as calcipotriene with corticosteroids in the context of sequential therapy is now widely practiced in the treatment of psoriasis. The utility of this approach has also been clearly demonstrated in recent trials.

As developed in clinical trials, sequential therapy involves three phases (Table 1).<sup>1,2</sup> The first phase, called the clearance phase, consists of short-term daily therapy with two topical agents. For example, a class I corticosteroid might be applied once or twice daily, followed by application of calcipotriene. Patients whose lesions respond to this daily combination therapy then enter the second or transition phase. During this phase, the use of the topical steroid is reduced from daily application to use only on weekends, while calcipotriene is applied

| Clearance Phase   | Transition Phase                     | Maintenance Phase        |
|---|--------------------------------------|--------------------------|
| 2 weeks-1 month   | 1-6 months (or longer)               | Prevention of recurrence |
| Class I corticosteroid (e.g., halobetasol, clobetasol) q.d. or b.i.d. | Corticosteroid b.i.d., weekends only | Discontinued             |
| Calcipotriene b.i.d.  | Calcipotriene b.i.d., weekdays only  | Calcipotriene b.i.d.     |

**Table 1:** Phases of sequential therapy

on weekdays, hence the terms “weekday-weekend” or “pulse” therapy. The length of this phase varies; recent trials describing sequential therapy for psoriasis have reported results extending up to 6 months, but longer duration of treatment may be indicated to prevent recurrence in some patients. Eventually, for the third or maintenance phase, only a non-steroid, namely calcipotriene, is used until the lesions clear completely.

### *Clinical Trials of Sequential Therapy*

The technique of pulse therapy was developed in placebo-controlled trials over a decade ago. Katz and colleagues, for example, evaluated the use of betamethasone for extended maintenance therapy.<sup>3</sup> Following short-term, twice-daily treatment for 2-3 weeks, 38 of 59 enrolled subjects achieved 85% improvement from baseline and were rolled into the second phase of the study. Thereafter, subjects were randomized to weekend use of either betamethasone or placebo. Seventy-four percent of the betamethasone group and 21% of the placebo group maintained clinical remission for 12 weeks, suggesting that pulse dosing was safe and efficacious for long-term treatment.

### *Combination Therapy: Calcipotriene With Corticosteroids*

Some years later, following the introduction of calcipotriene, investigators focused on the addition of this vitamin D analog to sequential therapy with corticosteroids. Lebwohl and colleagues evaluated the daily use of both calcipotriene and halobetasol for the sequential treatment of mild-to-moderate psoriasis.<sup>4</sup> After 2 weeks of daily combination therapy (i.e., clearing phase), 40 of 44 subjects demonstrated 50% or greater improvement, and were randomized to one of two groups: weekend halobetasol therapy with either weekday calcipotriene or weekday placebo.

Through 6 months of treatment, 76% of subjects in the calcipotriene group maintained remission, compared with 40% of those in the placebo group (p=0.045). The results of this trial clearly demonstrated that calcipotriene in combination with a class I corticosteroid was tolerable to patients, and that this combination improved remission rates in the second phase of sequential therapy.

Other investigators have also demonstrated that combination therapy with calcipotriene and corticosteroids is more efficacious than monotherapy.<sup>5</sup> Calcipotriene is moderately effective as a topical agent, and benefits from combination with other agents to maximize efficacy, particularly for initial treatment (i.e., the clearance phase of sequential therapy). The reasons for improved efficacy in combination with steroids are likely multifactorial. Steroids and vitamin D analogs act through different mechanisms of action that may be complementary. Corticosteroids have anti-inflammatory, immunosuppressive, antimitotic, and antipruritic actions, whereas calcipotriene reduces keratinocyte proliferation and acts as an immunomodulator. The side-effects of each agent also can be reduced through combination use. Because calcipotriene is safe for long-term use, it is an ideal agent for weekday use in combination with weekend steroid therapy, thus allowing for improved efficacy and reduced steroid side-effects. Furthermore, the most common side-effect of calcipotriene – irritation – may be reduced through concomitant use of topical steroids. Calcipotriene, therefore, is an ideal candidate for use with steroids in sequential therapy. The recent advent of combination agent calcipotriene + betamethasone (Dovobet®, LEO Pharma) also makes the use of the calcipotriene-corticosteroid combination easier. Dovobet® is approved for use in Canada and LEO Pharma, in conjunction with Warner Chilcott submitted an NDA to the US FDA in March 2005.

However, some authors have suggested that extemporaneous compounding of calcipotriene with other agents, such as steroids, may result in the degradation of the vitamin D analog.<sup>5</sup> Data from several sources should minimize this concern. One *in vitro* study showed no enhanced degradation of calcipotriene when used immediately after application of a steroid foam.<sup>6</sup> The results of recent clinical trials also indicate improved efficacy, rather than degradation, when calcipotriene is combined with topical steroids (see below).<sup>7</sup>

### *New Steroid Formulations and Sequential Therapy*

New formulations of topical steroids have proliferated in recent years. Among these formulations is the introduction of foam vehicles such as the clobetasol propionate foam (Olux™, Connetics). This foam is a thermolabile vehicle that breaks down on contact with human skin and at body temperature, providing for convenient and elegant application. Data from a variety of *in vitro* studies indicate that this foam formulation is a more efficient vehicle for drug delivery than other topical formulations, including both creams and ointments.<sup>8-11</sup> Furthermore, because clobetasol foam is quickly absorbed and leaves no residue, it is an ideal vehicle for use in combination with other topical agents, such as calcipotriene. This relative lack of concern regarding incompatibility applies only to the foam vehicle agent and not to any other situation where the vehicle does not vanish.

The utility of this combination – clobetasol foam and calcipotriene – was evaluated in a recently completed clinical trial of topical sequential therapy. The results of this trial were presented in two abstracts at the 2004 and 2005 meetings of the American Academy of Dermatology (AAD).<sup>7,12</sup> Part 1 of the study evaluated the twice-daily use of clobetasol foam and calcipotriene for the clearance phase of therapy.<sup>7</sup> Eighty-six subjects were randomized to three groups: combination therapy, or monotherapy with either clobetasol foam or calcipotriene. Subjects in the combination group were directed to apply calcipotriene immediately after the clobetasol foam was absorbed. After 2 weeks of treatment, reductions in psoriasis severity scores for target lesions were significantly greater in the combination therapy group than in either monotherapy group:

- vs. clobetasol:  $p=0.0017$  for trunk lesions,  $p<0.0001$  for extremity lesions

- vs. calcipotriene:  $p<0.0001$  for both trunk and extremity lesions.

As mentioned previously, the results also support *in vitro* data suggesting that degradation of calcipotriene does not occur when it used immediately following application of a topical steroid.<sup>6</sup>

At the 2005 AAD meeting, the results of the second phase of this trial were reported.<sup>12</sup> In this part – the second phase of the sequential treatment approach – subjects who achieved at least 50% improvement in target lesions during part one were randomized to one of two groups: weekday calcipotriene b.i.d. with weekend use of either clobetasol foam (b.i.d.) or placebo. Through 6 months of treatment, the combination therapy group showed a consistent, although not statistically significant trend toward greater maintenance of remission compared with the monotherapy group. Because this trend was similar for all assessments used in the study, the authors suggested that there may be a positive effect associated with the combination of clobetasol foam and calcipotriene in pulse therapy. Given the consistency of these trends, it is possible that the results would have been statistically significant if a greater number of subjects had participated in the study ( $n=38$ , intent-to-treat population).

### *Conclusions*

Topical sequential therapy is an accepted and widely practiced technique for rapid clearance of lesions and long-term maintenance of remission. This approach is a fruitful balance between maximizing efficacy and minimizing side-effects. Current sequential therapy paradigms are rooted in the synergistic effects of topical agents with different mechanisms of action and divergent side-effect profiles, in particular, the use of a class I corticosteroid with calcipotriene. Used together in daily application of the clearance phase, these agents complement one another and promote the rapid induction of remission. Subsequent weekend steroid therapy combined with weekday calcipotriene reduces the potential for steroid-related side-effects while improving the maintenance of remission. Patients who remain stable may then be switched to the third phase of sequential therapy, consisting of monotherapy with daily calcipotriene. Recent clinical trials support this approach. Newer steroid formulations, namely foam vehicles, further improve the convenience and efficacy of sequential therapy, eliminating concerns regarding dilution and incompatibility through their rapid evaporation.

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# Approaches to Treatment of HIV Facial Lipoatrophy

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## ABSTRACT

*HIV-associated facial lipoatrophy has become epidemic among the greater than 1 million HIV-infected individuals living in the United States. Those affected usually have well-controlled HIV disease, and are most often healthy and living productive lives. However, their facial appearance often suggests the opposite and frequently serves as a stigma and psychological burden. Treatment approaches may be divided into three categories: 1) Surgically placed alloplastic, autologous, or synthetic implants; 2) Injection of temporary fillers; 3) Injection of permanent fillers, including liquid injectable silicone. Salient aspects of each treatment are reviewed, along with new techniques and pearls on the correct use of liquid injectable silicone.*

**Key Words:** *HIV, facial lipoatrophy, implants, temporary fillers, permanent fillers*

Although HIV facial lipoatrophy is associated with the use of certain antiretroviral drugs, including indinivir (Crixivan<sup>®</sup>, Merck) and stavudine (Zerit<sup>®</sup>, Bristol-Myers Squibb), it is clearly not exclusively a drug effect. Risk factors include:

- being Caucasian
- being >40 years of age
- having an HIV infection for >10 years
- having a CD4 of <100 or <100 at nadir
- taking indinivir for >2 years
- any use of stavudine.<sup>1</sup>

HIV facial lipoatrophy may be caused by cytokine alterations associated with living long-term with HIV. In patients experiencing rapid progression of HIV facial lipoatrophy and also taking indinivir and/or stavudine, alternative drug regimens should be considered. Once lipoatrophy has appeared, it seems that no systemic therapy will reverse the fat loss to an appreciable extent. The most effective treatment is soft tissue augmentation.

### *Surgical Alloplastic, Autologous, or Synthetic Implants*

Autologous fat transfer for HIV facial lipoatrophy has been attempted.<sup>1</sup> However, because subcutaneous lipoatrophy also occurs in the abdominal and buttock area, most patients lack adequate donor fat reserves.

Furthermore, transferred fat often continues to dwindle, and corrections often fade over 6-12 months.

Surgical grafting of autologous dermis with attached subcutaneous fat has also been attempted (dermafap grafts). Surgical implantation of cadaveric dermal grafts (such as regenerative tissue matrix, AlloDerm<sup>®</sup>, LifeCell) provides short-term augmentation, with most grafts becoming reabsorbed within 2 years. Recently, the use of custom-designed silastic implants was described.<sup>2</sup> Drawbacks include a rigid feel beneath the skin, and exposure of implant edges should lipoatrophy progress. All of these surgical options are associated with surgical downtime, and high cost, which limit their attractiveness.

### *Injectable Temporary Fillers*

Collagen (bovine or human) or hyaluronic acid may be used to augment the subcutis, but the volumes required to correct HIV lipoatrophy are usually cost prohibitive. The most reasonable temporary filler for HIV facial lipoatrophy may be the newly approved poly-L-lactic acid (Sculptra<sup>®</sup>, Dermik). Poly-L-lactic acid is a synthetic absorbable material that stimulates a fibroproliferative response upon injection in the subcutis. Often five or more treatments, spaced at 2-week intervals, are required to treat HIV facial lipoatrophy. Optimal corrections may persist for 1-2 years, at which point reinjection is necessary. The biggest drawback, as with other temporary fillers,

is the high cost. Treatments (2 vials per treatment) generally will cost the patient \$1500 USD or more per treatment session. Obtaining insurance reimbursement is often difficult or impossible, and patients often find the treatments financially out of reach. Dermik has recently instituted a patient assistance program whereby patients making under \$40,000 yearly may qualify for free product, but the patient is still responsible for the physician fee, which is often \$500 or more per injection session. It should also be noted that in European studies, up to 44% of patients developed palpable but non-visible subcutaneous micronodules, which tended to spontaneously resolve.<sup>3</sup> Persistent granulomatous dermal papules have been observed, and may be caused by inadvertent intradermal injection.<sup>1</sup>

### *Injectable Permanent Fillers*

Among patients with HIV facial lipoatrophy, there has been great demand for permanent injectable fillers. At this point, the only injectable permanent filler legally available in the United States is liquid injectable silicone. Although not specifically approved for soft tissue augmentation, Silikon™ 1000 is FDA-approved for intraocular injection for tamponade of retinal detachment, and may be used legally on an off-label basis for subdermal volume restoration. Recently, Silikon™ 1000 was described as a safe and effective method for treatment of HIV facial lipoatrophy, although long term safety and efficacy have yet to be established.<sup>4</sup>

There is controversy surrounding the use of liquid injectable silicone. Critics believe that liquid injectable silicone is inherently unpredictable, with an unacceptably high incidence of complications such as nodule formation or inflammatory reactions appearing sometimes many years after injection.<sup>4</sup> Advocates, however, rely on a wealth of anecdotal data<sup>4</sup> to support the claim that liquid injectable silicone is safe and predictable as a soft tissue filler, and that complications are very rare as long as the following three rules are obeyed:

1. Use pure injectable grade silicone which is US FDA approved for injection into the human body. It is noteworthy that prior to the mid 1990s, no such injectable grade silicone existed for routine use. An analysis of liquid injectable silicone oils often used for tissue augmentation in the 1960s, 1970s, and 1980s revealed an excess of impurities, which may account for instances

of inflammatory reactions related to silicone injections during that time.

2. Adhere to strict serial puncture microdroplet technique, with injections only into the subdermal plane or deeper. Intradermal injections are to be avoided, as dermal swelling, erythema and ridging may result. Silikon™ 1000 should be injected through a 30G Max-Flo® needle (Richard James Development) with approximately 0.01cc injected with each needle insertion, at approximately 2-5mm intervals. Over a period of several weeks, a limited foreign-body response causes each microdroplet to be enveloped by a collagenous capsule. This promotes further tissue augmentation and allows each microdroplet to be anchored in place, obviating the risk of migration.
3. Inject limited volumes at monthly intervals. Injection of large volumes all at once increases the risk for migration along tissue planes, as a bolus of silicone oil will not immediately anchor itself to the surrounding tissue. The protocol for HIV lipoatrophy calls for no more than 2ccs to be injected at monthly intervals. Approximately three treatments will be required for each stage on the Carruthers' lipoatrophy severity scale.<sup>4</sup> Therefore, a stage 1 patient will require an average of three treatments, a stage 2 patient an average of six treatments, and a stage 3 patient an average of nine treatments. This is merely a guideline, but is useful in counseling patients during the consultation process. Patients should also be counseled that the correction proceeds very gradually, but that eventual optimal correction is expected in vast majority of patients.

### *Injection Pearls for Liquid Injectable Silicone*

After a consultation where risks, benefits, indications and options of liquid injectable silicone are reviewed, appropriate informed consent and high quality photos should be obtained. The patient should refrain from taking aspirin, NSAIDS, and vitamin E for 7-10 days prior to treatment.

The patient's face is cleansed with povidone iodine or an antibacterial cleanser. Topical anesthetic cream (benzocaine 20%, lidocaine 6%, tetracaine 4%) is applied under plastic occlusion to the areas to be treated for at least 30 minutes. The topical anesthetic is then removed with gauze. Using a new fine tip Sharpie black pen, areas to be injected are carefully outlined. This is perhaps the most important, and potentially the

most difficult, aspect of treatment planning. Areas of depression at rest often tend to become elevated when the patient smiles, depending on tissue redundancy. Therefore, the author finds it most useful mark the patient first in a smiling position. While the patient smiles, the areas of greatest depression are carefully outlined with the pen in the malar, pre-masseteric, pre-auricular, and temporal areas. Then, with no smile, areas of deepest depression are carefully marked. It is important to assess where areas of depression at rest may be potentially overcorrected in such a way that excessive elevation occurs while smiling. In those areas, appropriate caution and conservative volumes should be employed to avoid overcorrection.

Once marking is complete, injections may begin. Silikon™ 1000 should be injected strictly into the subdermal plane or deeper. The most common mistake among novice injectors is injecting intradermally, which is likely to produce a suboptimal result and complications including dermal edema and erythema. Injections should be performed at 2-5mm intervals throughout the entire marked area. Volumes should be limited to 2cc total per treatment session. A second pass may be taken in the deepest areas, about 5mm deeper than the first pass. Generally, there is mild, even swelling after the procedure which the patient frequently enjoys, and which resolves within 3-7 days.

Many patients like the slow, gradual correction, as the transformation is not drastic and therefore not obvious to those with whom they interact more frequently.

Performed correctly, injection of liquid injectable silicone offers an extremely cost effective, very natural feeling, and durable correction of HIV facial lipoatrophy. Currently, about 1000 patients have been treated at four centers using this protocol, with no severe adverse events over 4 years.<sup>4</sup> However, patients should be counseled that this is still considered an investigational treatment, and that longer term data are necessary to more completely understand the long-term disposition of this permanent filler in the HIV patient.

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| Class                 | Name/Company   | Approval Dates and Comments   |
|-----------------------|--|---|
| <i>Antihistamines</i> | <b>Desloratadine</b><br><i>CLARINEX® REDITABS®</i><br>Schering-Plough                                | The US FDA approved these reformulated 2.5mg and 5mg tablets in July 2005 for the treatment of allergy symptoms caused by both perennial indoor and seasonal outdoor allergens, and chronic idiopathic urticaria, or hives of unknown cause in adults and children >6 years of age. This formulation dissolves without water.   |
| <i>Antiacne Agent</i> | <b>Dapsone</b><br><i>ACZONE™ Gel 5%</i><br>QLT   | The US FDA approved this topical gel in July 2005 for the treatment of acne vulgaris.   |
| <i>Rosacea</i>        | <b>Metronidazole</b><br><i>Metrogel® Topical Gel 1%</i><br>Dow Pharmaceutical Sciences/ Galderma     | The US FDA approved this topical product in July 2005 for the treatment of inflammatory lesions of rosacea.   |
| <i>Vaccines</i>       | <b>Measles, Mumps, Rubella and Varicella Vaccine</b><br><i>Proquad®</i><br>Merck/ Sanofi Pasteur MSD | The US FDA approved this live attenuated viral vaccine in September 2005 for simultaneous vaccination against measles, mumps, rubella, and varicella in children 12 months to 12 years of age. Also in September 2005, the Committee for Medicinal Products for Human Use adopted a positive opinion and recommended that marketing authorization be granted in Europe. |

| Drug News                           |   |
|-------------------------------------|---|
| <i>Hypertrichosis and Hirsutism</i> | Barrier Therapeutics announced in June 2005 that it has acquired the right to distribute VANIQA® (eflornithine) 13.9% cream in Canada from Shire Pharmaceuticals. Marketing is expected to begin in October 2005. VANIQA® is approved by Health Canada for slowing the growth of unwanted facial hair in women by blocking an enzyme that is necessary for hair growth during the growth phase of the hair cycle. Clinical trials have shown positive results after 4-8 weeks of use with continued improvement over time.  |
| <i>Case study</i>                   | According to a case study in the <i>New England Journal of Medicine*</i> , a 62-year-old woman had progression of multiple myeloma despite many therapies, including an autologous hematopoietic stem-cell transplantation. Infusions of bortezomib (1.3mg/m <sup>2</sup> of body surface area) were administered as an IV bolus twice weekly for 2 weeks, followed by a 10-day rest period. During the second treatment cycle, a purpuric rash, not associated with fever or itching, developed on the patient's trunk, back, hands and face. Biopsy of the skin lesion revealed a leukocytoclastic vasculitis. The patient was treated with 20mg prednisone, and the rash resolved. The rash recurred with subsequent cycles of bortezomib treatment.<br><i>*N Engl J Med 352(24):2534 (2005 Jun 16).</i> |
| <i>Vaccines</i>                     | In one of the largest adult vaccine clinical trials ever, researchers have found that an experimental vaccine against shingles (ZOSTAVAX™, Merck) reduced the incidence of shingles by 51% and dramatically reduced its severity and complications in vaccinated persons who got the disease. The randomized, double-blind, placebo controlled trial was conducted at 22 study sites throughout the US with 38,500 men and women aged >60 years in order to determine whether vaccination with a single dose of this live attenuated vaccine would reduce the incidence and/or severity of shingles.*<br><i>*N Engl J Med 352(22):2271-84 (2005 Jun 2).</i>   |

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