Topical Retinoids in the Treatment of Acne Vulgaris

Introduction

The dermatology community recognizes the psychosocial impact that acne has on patients' lives, and the need for adequate and early treatment to optimize quality of life and minimize the risk of scarring.[1] With the recent developments in topical retinoid treatments for acne, it is timely to review our current state of knowledge of this aspect of dermatology.

Retinoids have important effects on the growth and differentiation of cells,[2] and offer effective treatment for a wide variety of dermatological and oncological conditions in which cellular growth or differentiation is abnormal. There are currently 3 topical retinoids indicated for acne vulgaris in the USA—tretinoin, adapalene, and tazarotene. In addition, topical isotretinoin and retinaldehyde are available in many countries outside of the USA. We can likely look forward to an even greater choice of retinoids in the future as our ability to relate the functional characteristics of different retinoids to their chemical structure advances, so helping us design molecules with even better efficacy, tolerability, and/or safety profiles than those currently available.

Now that we have a menu of topical retinoids from which to choose, the relative merits and drawbacks of these agents are important factors in making therapeutic decisions. To discuss these merits and drawbacks, a group of 11 dermatologists took part in a roundtable discussion of topical retinoid therapy for acne on May 15, 1999, in Chicago, Illinois. This publication summarizes the discussions at the meeting, with the aim of helping physicians everywhere further their expertise in treating acne vulgaris.

The Evolution of Topical Retinoids for the Treatment of Acne

Tretinoin (the endogenous retinoid, all-*trans*-retinoic acid) first became available more than 25 years ago and has been used to treat acne vulgaris ever since. However, local skin irritation has sometimes limited patients' ability to utilize this medication for the long time periods required for successful treatment.[3] In an attempt to overcome this problem, a variety of different formulations of tretinoin and its isomer, isotretinoin (13-*cis*-retinoic acid), have been developed that aim to lessen skin irritation without compromising efficacy.[4-7] Some studies suggest that topical isotretinoin improves tolerability without affecting efficacy.[8] However, Dr Shalita believes that the consensus view among European dermatologists (where isotretinoin is available in a topical formulation) is that, in everyday clinical practice, the improved tolerability is also accompanied by reduced effectiveness.

Research efforts have focused not only on developing less irritating formulations of tretinoin, including a gel microsphere formulation and a formulation in which tretinoin is complexed to a polymer, but also on synthesizing new molecules that are inherently less irritating. The discovery and characterization of retinoid receptors, beginning in 1987,[9,10] paved the way for chemists to design retinoids, such as tazarotene and adapalene, that are selective for specific retinoid receptors. Whereas tretinoin binds to α-, β-, and γ-retinoic acid receptors (and isomerizes to 9-*cis*-retinoic acid, which binds weakly to the RXR receptors), tazarotene and adapalene are selective for β- and γ-retinoic acid receptors.[11,12] Tazarotene and adapalene are the only 2 receptor-selective retinoids currently available, although others are in early stages of clinical development. It is hypothesized (though not proven) that receptor selectivity may help limit the potential for adverse effects arising from activation of retinoid pathways that are unrelated to the pathogenesis of acne vulgaris. However, the predominant retinoic acid receptor expressed in the skin—and probably the most important for acne—is the γ-subtype, and tretinoin has higher affinity for γ-retinoic acid receptors than either tazarotene or adapalene. Furthermore, from a practical point of view, irritation from different retinoids appears

to be more dependent on their formulation rather than their receptor selectivity.

Which Patients Are Candidates for Topical Retinoid Therapy?

There is a tendency for dermatologists to think of retinoids, and particularly topical retinoids, as being effective only in non-inflammatory lesions of acne vulgaris, according to Dr Leyden. However, as he explained, topical retinoids help to correct the abnormal desquamation of follicular epithelium that leads to the formation of microcomedones—which are the precursors of both non-inflammatory and inflammatory lesions. Therefore, by improving the microenvironment, topical retinoids are useful in helping to resolve and prevent both non-inflammatory and inflammatory acne lesions. Furthermore, by helping to normalize the desquamation process, topical retinoids facilitate the penetration of other topical anti-acne agents.

Dr Brodell warned against using topical retinoid therapy on the extremely sensitive skin of patients with acne and "topical steroid addiction syndrome" (steroid-induced perioral dermatitis; Figure 1) until the patient's dependence on the steroid is resolved and post-withdrawal erythema, scaling, and pruritus have quieted. (Dr Brodell helps break this dependence using erythromycin or tetracycline, 500 mg b.i.d., with clindamycin phosphate 1% lotion, b.i.d. or t.i.d., and pramoxine hydrochloride 1% lotion as a moisturizing anesthetic, warning patients to expect a worsening of their condition for up to 10 days following the discontinuation of the topical steroid before they begin to get better.) Once the "steroid addiction syndrome" is resolved, topical therapy with tazarotene or tretinoin is highly appropriate due to the ability of these retinoids to reduce steroid-induced atrophy. Tazarotene has been demonstrated to reduce steroid-induced atrophy in healthy volunteers,[13] and tretinoin has demonstrated such effects in patients with psoriasis[14] as well as in mice.[15,16]

Efficacy of Topical Retinoids

European dermatologists are in a good position to judge the relative efficacy of the different topical retinoids as they have topical isotretinoin available and they have a longer experience with using adapalene. According to Dr Shalita, their general view is that adapalene is more effective than isotretinoin, but is less effective than tretinoin and is not for recalcitrant acne.

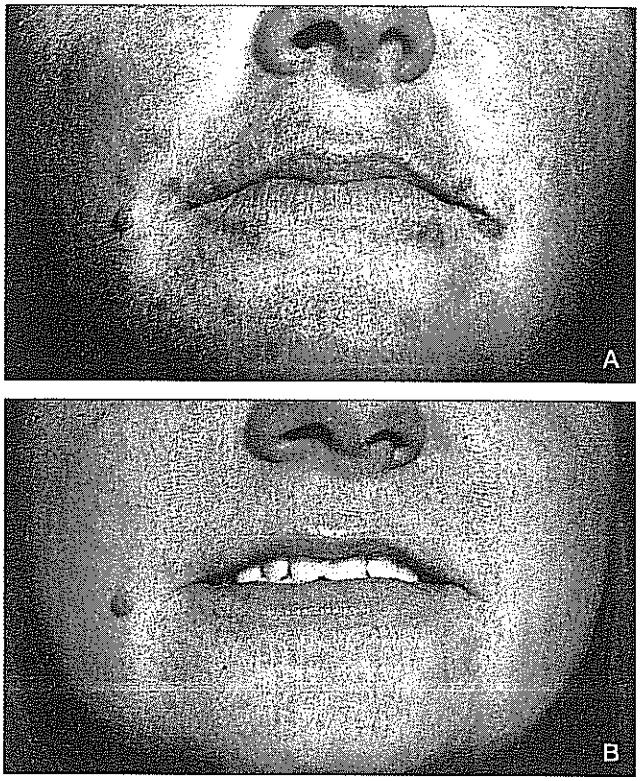

Figure 1. Topical treatment with tazarotene or tretinoin may be useful in reducing steroid-induced atrophy in patients with acne who have developed "steroid addiction syndrome" (Figure 1A). Because of the skin's irritability, it is important to resolve the steroid addiction first (Figure 1B) before initiating topical retinoid treatment. In this patient, the steroid dependence was resolved with the aid of clindamycin phosphate 1% lotion b.i.d. and pramoxine hydrochloride 1% lotion as a moisturizing anesthetic. *Photographs courtesy of Dr Robert Brodell.*

Adapalene versus tretinoin

Although a meta-analysis of clinical trial data suggests that the efficacy of adapalene 0.1% gel is comparable to that of tretinoin 0.025% gel,[17] most—though not all—of the dermatologists at the roundtable meeting were of the opinion that tretinoin is actually more effective than adapalene in everyday clinical practice. Furthermore, unlike adapalene, tretinoin is available formulated in more than 1 concentration and vehicle, and thus offers greater therapeutic flexibility. When the efficacy of 2 drugs can be differentiated in clinical practice, but not in clinical trials, it is possible that the type of patients studied in the trials are not representative of those being treated in clinical practice. Dr Shalita believes that studies recruiting patients from advertisements, rather than from office patients, are likely to attract patients who have not yet tried any or many of the available treatment options—so-called "virgin acne" patients—and that these patients are far more likely to respond to any type of acne treatment, even over-the-counter treatments,

than the patients who are more typically seen in a dermatologist's office. This is because patients visiting a dermatologist are far more likely to have already tried—and failed to respond to—the available over-the-counter treatments, and this "pre-screening" means they are likely to have tougher-to-treat acne. As a result, studies involving patients who have not yet tried many of the available treatment options may suggest greater efficacy than that which is often achieved in clinical practice, and, in addition, such studies may be unable to demonstrate differences in efficacy between 2 drugs that seem to exist in everyday clinical practice. Again, this belief was shared by some—though not all—of the dermatologists at the roundtable meeting.

Tazarotene versus tretinoin

Tazarotene 0.1% gel has been compared with tretinoin 0.025% gel in a multicenter, double-blind, randomized, parallel-group trial involving patients with mild-to-moderate acne vulgaris who were treated for up to 12 weeks with tazarotene q.d. or tretinoin q.d. Preliminary data from the 109 patients evaluated to date were presented for the first time at the roundtable meeting. The results suggest that the tazarotene treatment is more efficacious than the tretinoin treatment in reducing the numbers of papules and open comedones (Figure 2), and achieves a more rapid reduction in pustules. Both drugs were equally efficacious in reducing the number of closed comedones.

Dr Kakita noted from her experiences performing acne surgery that tazarotene seems to be able to prevent the formation of new comedones more effectively than tretinoin. Further research is required to verify this observation.

Tazarotene versus adapalene

Tazarotene 0.1% gel has been compared with adapalene 0.1% gel in a multicenter, double-blind, randomized, parallel-group trial and preliminary data from this trial were presented for the first time at the roundtable meeting. In this trial, tazarotene 0.1% gel q.o.d., applied on alternating evenings with vehicle gel on the intervening evenings, was compared with adapalene 0.1% gel q.d. over a period of 15 weeks in patients with moderately severe acne (mean open and closed comedone count of 58, and mean papule and pustule count of 26, at baseline). The preliminary data from the first 87 patients suggest that, even though tazarotene was applied only half as often as adapalene (q.o.d. versus q.d.), both treatments achieved comparable reductions in non-inflammatory and inflammatory lesion count, and comparable reductions in overall disease severity (Figure 3).

Tolerability of Topical Retinoids

Tretinoin

The frequency of tretinoin application is usually once daily, throughout the course of treatment, so dose titration is often achieved by gradual progression from the low concentration formulations to the higher concentration formulations. In particularly sensitive patients, it may be advisable to initiate therapy with every other day applications and then to increase to daily applications. Occasionally, the frequency of application is increased to twice daily.

The tretinoin gel microsphere formulation and the tretinoin polymer formulation offer alternative approaches to earlier tretinoin gel formulations. These

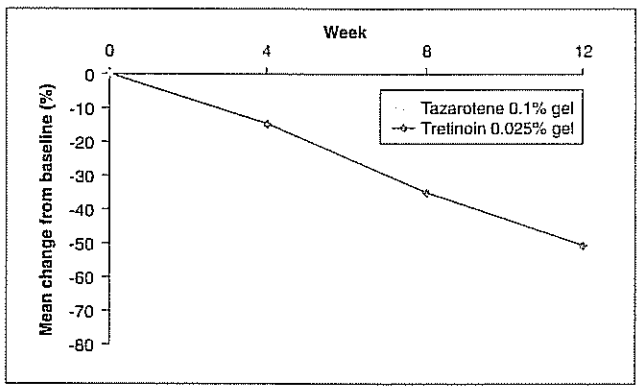

Figure 2. Mean percentage reduction in open comedo count in patients with facial acne vulgaris during 12 weeks of treatment with tazarotene 0.1% gel q.d. or tretinoin 0.025% gel q.d.

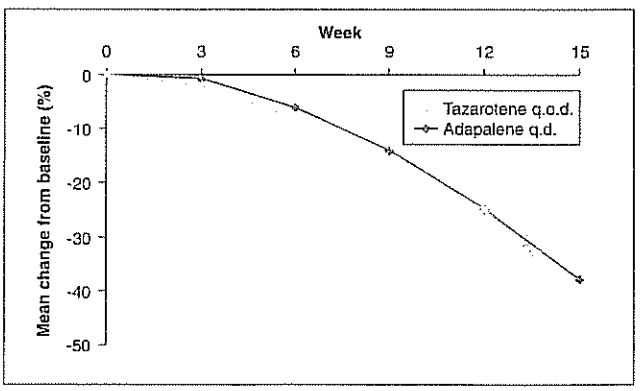

Figure 3. Mean percentage reduction in overall disease severity score in patients with facial acne vulgaris during 15 weeks of treatment with tazarotene 0.1% gel q.o.d. or adapalene 0.1% gel q.d.

formulations aim to limit irritation through follicle-targeted delivery of tretinoin and modified delivery of tretinoin in the skin, respectively.

Adapalene

Although adapalene is commonly believed to be one of the least irritating topical retinoids, the perception of many dermatologists is that this advantage is at least partially negated by a relatively lower efficacy compared with the other topical retinoids. Some dermatologists indicated that they never used adapalene because of this perception of relatively inferior efficacy, whereas others indicated that its mildness means that they may use it as first-line therapy in particularly dry and cold weather, and in patients with particularly sensitive skin. This milder product, utilized over an extended period, can lead to successful treatment that may not be achievable with a less well tolerated, more irritating product.

Tazarotene

Dr Poulin reported that, contrary to the initial expectations of many, tazarotene is surprisingly well tolerated in acne and patients rarely complain of dryness or skin irritation, even in dry, cold climates. Reporting the results of his photographic tracking study of tazarotene (q.d. or q.o.d.) or tretinoin (q.d.) treatment of acne vulgaris, Dr Poulin observed that few of the 42 patients in the study reported being bothered by dry skin, and those who did tended to be those with Fitzpatrick skin type 1 or 2. Dry skin was controlled by using a moisturizer in the mornings, and no patients discontinued the treatment because of dry skin.

Drs Shalita and Leyden urged dermatologists to disregard what they know of the tolerability of tazarotene from their clinical experiences with psoriasis on the body. As with tretinoin, which is not well tolerated in all patients with psoriasis, we cannot extrapolate what we might expect to happen in acne from what we know from psoriasis. As they explained, this is because acne is a different disease and affects different areas of the body. In psoriasis, the skin's barrier function is compromised and the fissures and microscopic cracks in the stratum corneum can enhance epidermal penetration. The resultant increase in drug delivery increases the potential for irritation. Another distinguishing feature of psoriasis is that even apparently uninvolved skin shows pathologic abnormalities. In contrast, in acne, the skin retains its barrier function and the pathogenic changes remain confined to specific areas of the body. The high density of sebaceous glands in these acne-prone areas may help to enhance the tolerability of topical retinoid therapy by increasing sebum levels on the skin surface. This combination of higher sebum levels and an intact stratum corneum promote greater tolerability.

Tazarotene versus tretinoin and adapalene

In the previously mentioned tazarotene versus adapalene trial, tazarotene treatment was associated with slightly higher transient increases in peeling, erythema, and dryness during the early weeks of treatment, compared with adapalene treatment. However, as mean maximum levels of these parameters were consistently only of mild severity or less in both groups, this is generally of minimal clinical significance. (Nevertheless, in cold, dry climates, increased irritation may be more problematic.)

In the trial comparing tazarotene with tretinoin, both treatment groups experienced peeling, erythema, and dryness at only trace levels or less throughout the study.

Short-contact method of applying tazarotene

A newly developed short-contact method of applying tazarotene offers patients an alternative approach to applying their acne medication. This experimental method has been developed by Dr Bershad and involves applying a pea-sized amount of tazarotene gel to the facial skin for up to 5 minutes at a time, avoiding the eye area and the lips, and then washing the gel off with warm water. Dr Bershad has achieved moderate (50% to 75%) to marked (greater than 75%) improvement within 2-3 months in more than 60% of patients using her short-contact method of applying tazarotene gel. Furthermore, the vast majority of her patients find such treatment to be pleasant and convenient.

The method allows relatively aggressive therapy (twice-daily applications) to be initiated with only a minimum of tolerability problems due to the limited time that the skin comes into contact with the tazarotene gel. Therapy is usually initiated with a contact time of 2 minutes. If irritation occurs within the first few days, the contact time is reduced to 30 seconds and gradually increased to 2 minutes, as tolerated. If no discomfort is experienced, the contact time can be increased to a maximum of 5 minutes, by adding 1 minute every 3 days.

As with other topical retinoid therapies, a small percentage of patients may experience a pustular flare during the first few weeks of therapy, giving the appearance of temporarily worsening acne. Patients should be warned of this potential effect and reassured that it is not only transient but also an indication of the effectiveness of therapy. It is thought that a 10- to 14-day course of an oral antibiotic at the onset of therapy may help prevent such a pustular flare, although this remains to be proven.

The short-contact method is suitable for all skin types and, because of the short contact times, has even been used successfully in patients with highly sensitive type 1 skin who might otherwise not be good candidates for topical retinoid therapy. With a contact time of only 30 seconds, Dr Bershad has also successfully treated patients with atopic dermatitis. In any patient, some irritation may still arise and "hand-holding" may be necessary at first, but approximately 95% of all her patients with acne seem to tolerate the short-contact method.

Although further studies are required to confirm these observations, Dr Bershad has found that many patients prefer this method of application to the traditional method of leaving the gel on the skin, because they prefer not to have acne medication on their skin all day (male patients in particular tend to dislike the feel, texture, look, and odor of topical preparations on their skin) and like to be able to apply cosmetics and other skin products directly onto their skin. As a result, this method has found particular favor both with male teenagers (who do not like to leave medication on their skin) and adult women (who like to apply other skin products directly on their skin). If combination therapy is required, sequential therapy with other topical acne products is easily achieved.

This short-contact method of application remains experimental and fellow dermatologists await results of controlled clinical trials before adopting this method as a standard treatment regimen. The short-contact method has only been tried with tazarotene gel to date. However, if this method were to be tried with other topical retinoids, it is likely that the optimal duration of the short-contact treatment would vary depending on the pharmacokinetic and other characteristics of the particular retinoid formulation.

Safety of Topical Retinoids

Because of the physiological role that retinoids play in controlling the growth and differentiation of cells, it is not surprising that, with high enough systemic exposure, they can be teratogenic. Oral dosing of a retinoid may result in plasma retinoid levels rising high enough to cause a significant risk of teratogenicity. However, topical delivery of retinoids results in a far lower level of systemic exposure, due largely to the limited absorption of topical retinoids through the skin and into the bloodstream—plasma retinoid levels after topical treatment with tretinoin, tazarotene or adapalene have been shown to remain below the combined endogenous plasma levels of all-*trans*-retinoic acid, 13-*cis*-retinoic acid, and 13-*cis*-4-oxoretinoic acid (Table 1).[13,18-22] This indicates that any risk of teratogenicity with topical application of these products is minimal.

Available scientific evidence suggests that tazarotene has no greater teratogenic potential than tretinoin or adapalene, despite tazarotene being labeled as a Category X drug (which indicates that it may cause fetal harm when administered to a pregnant woman) and tretinoin and adapalene being labeled as Category C drugs (which indicates that their teratogenic potential is unknown). The difference in labeling stems largely from the fact that tazarotene is also indicated for the treatment of plaque psoriasis and, in this condition, could potentially be applied to a far greater percentage of the body's surface area than would be the case in facial acne. (In psoriasis, tazarotene is indicated for use on up to 20% of the body's surface area whereas, in facial acne, the generally smaller skin surface area precludes the need for any limit. Moreover, patients with extensive truncal involvement who may receive tazarotene treatment for acne on their face, chest, and upper back—which could potentially exceed 20% of their body surface area—are more likely to be male than female.) Even if tazarotene were to be applied to a greater skin surface area, the pharmacokinetic profile of the drug minimizes its systemic exposure which, in turn, minimizes any potential for teratogenicity. The 3 key pharmacokinetic features of tazarotene that contribute to minimizing its systemic exposure are: limited transcutaneous penetration into the bloodstream, rapid metabolism to hydrophilic metabolites (which helps prevent any retinoid absorbed into the blood from accumulating in adipose tissue), and rapid elimination of the metabolites from the body.[23]

Which Retinoid for Which Patient?

For each individual patient it is helpful to consider whether the first priority of treatment should be to maximize efficacy and speed of response, or to maximize tolerability. If maximum efficacy and speed of response are most important, then tazarotene or one of the higher concentration tretinoin formulations would be rational topical retinoid choices. However, patients should be advised of the slightly higher risk of experiencing transient local skin irritation in the first few weeks of treatment, compared with adapalene treatment. If tolerability is an issue, then adapalene or a low concentration tretinoin cream formulation would be a rational choice of topical retinoid. If patients are keen to keep their skin free of acne medication, then the experimental method of short-contact tazarotene therapy could be considered.

Table I

PLASMA RETINOID LEVELS AFTER TOPICAL OR ORAL RETINOID TREATMENT, COMPARED WITH ENDOGENOUS PLASMA RETINOID LEVELS.

Retinoid	Treatment conditions	Subjects	Mean post-treatment level of drug and metabolites (ng/mL)	Mean endogenous level of drug and metabolites (ng/mL)
All-*trans*-retinoic acid	Tretinoin (all-*trans*-retinoic acid) 0.05% or 0.1% cream topically q.d. for 28 days	Vol	2.60[16] –All-*trans*-retinoic acid + all metabolites–	Up to 7.67[19]
		Pt	2.60[13] ——— All-*trans*-retinoic acid ———	1.32-2.36[18,19]
		Pt	0.5[13] ——— 13-*cis*-retinoic acid ———	< 1.0-1.63[18,19]
		Pt	1.6[13] ——— 13-*cis*-4-oxoretinoic acid ———	3.68[19]
13-*cis*-retinoic acid	Isotretinoin (13-*cis*-retinoic acid) 80 mg orally	Pt	98-535[20]	< 1.0-1.63[18,19]
Adapalene	Adapalene 0.1% gel topically q.d. for 12 weeks	Pt	< 0.25[21]	0
Tazarotene	Tazarotene 0.05% or 0.1% gel topically q.d. for 12 weeks	Pt	0.06-0.22[22] ——— Tazarotene ———	0
		Pt	0.06-0.13[22] ——— Tazarotenic acid ———	0

Vol = healthy volunteers; Pt = patients with acne

For optimal therapy, tazarotene, tretinoin or adapalene treatment should be combined with oral or topical antibiotic therapy. Such combination treatment helps to normalize 2 of the 3 major pathophysiological features of acne—abnormal desquamation of follicular epithelium, proliferation of *P. acnes* and increased sebum production.

Patients with severe acne

Although tazarotene is specifically indicated for the treatment of mild-to-moderate acne vulgaris, most of the dermatologists at the roundtable meeting consider that both tazarotene and tretinoin can also be useful and effective in the treatment of severe acne, particularly when used in combination with oral antibiotic therapy.

Recalcitrant patients

All 3 topical retinoids are suitable as first-line treatment but the general opinion of the dermatologists at the roundtable meeting was that only tazarotene and tretinoin are likely to be effective enough to be clinically useful in refractory patients. Some dermatologists considered tazarotene to be particularly useful in patients with deep-seated, stubborn comedones and Dr Sabean recommended trying tazarotene before resorting to oral isotretinoin.

Patients with sensitive skin

Greater caution may be required when treating, and particularly when initiating treatment in, patients with sensitive skin. With careful initiation of therapy, however, topical retinoid therapy has been tolerated successfully in such patients. With tazarotene, the potential for irritation may be minimized by using Dr Bershad's short-contact method of application.

Patients with dark skin

Drs Kakita and Berson both reported that tazarotene seems to be particularly well tolerated in dark-skinned patients, such as African Americans. Drs Berson and Tanghetti both mentioned that tazarotene also appears to even out post-inflammatory hyperpigmentation in patients with skin type 5 or 6 (Figure 4), an effect that has also been observed by some dermatologists with tretinoin treatment and with adapalene treatment. Hydroquinone can also be useful in the treatment of post-inflammatory hyperpigmentation.

When oiliness of the skin is an issue

Tazarotene is particularly suited for use in patients with oily skin, and the generally good tolerability of tazarotene, and topical retinoids in general, in facial acne could well be partly attributable to the fact that the facial skin tends to be oilier than the skin in other areas of the body. Although tazarotene has not been shown to reduce sebum excretion, at least during the first few weeks of treatment (Leyden, unpublished data), patients do perceive that the oiliness of their skin decreases with tazarotene treatment. In patients with oily skin who did not respond to any other treatment, Drs Kakita, Brodell, and Berson all reported that they had found tazarotene gel, applied twice daily, to be successful in reducing the skin's oiliness. In the future, topical antiandrogenic

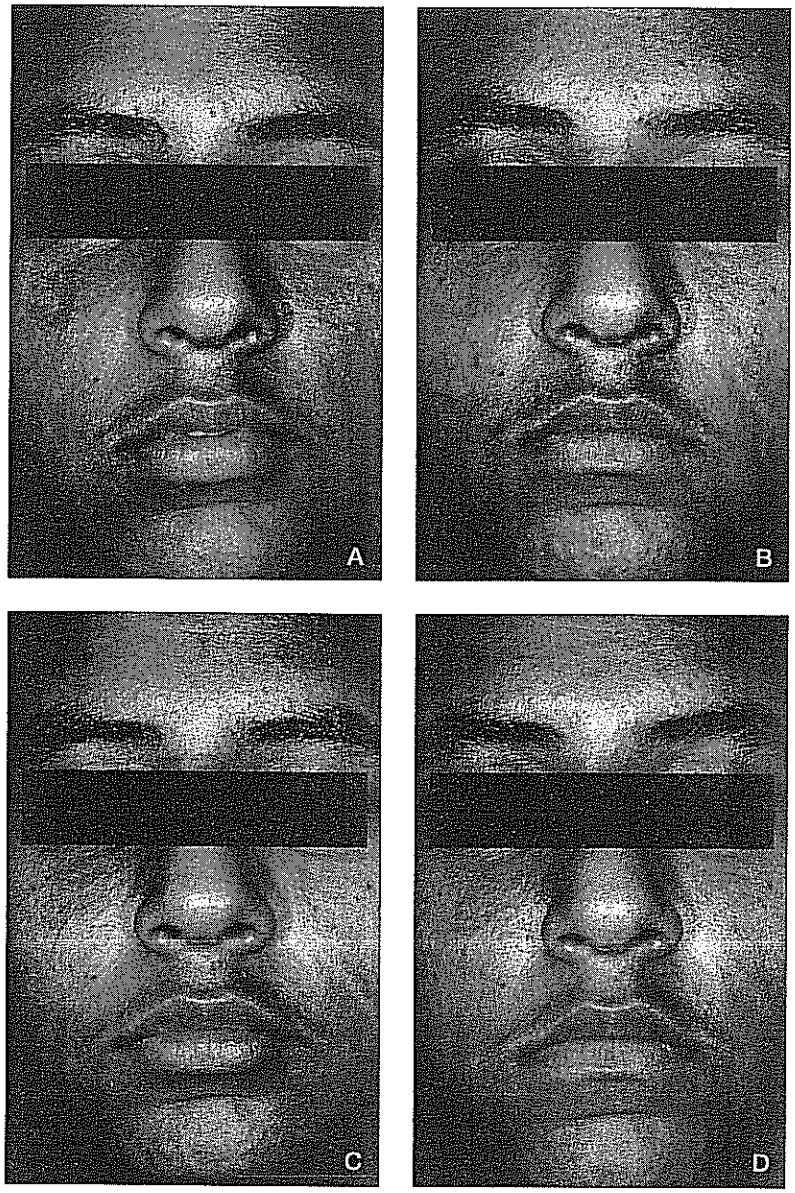

Figure 4. Evening out of mottled pigmentation with topical retinoid therapy. The patient was treated with tazarotene 0.1% gel, once daily, for 12 weeks. (A) Baseline; (B) After 4 weeks of treatment; (C) After 8 weeks of treatment; (D) After 12 weeks of treatment. *Photographs courtesy of Dr Emil Tanghetti.*

agents may be another treatment option available to reduce the oiliness of the skin.

When HMOs don't cover once-daily tazarotene treatment

Try every other day therapy. Dr Sabean reported that the only way he could get HMOs to cover tazarotene treatment for some of his patients was to prescribe it for every other day use. He found that this regimen worked extremely well in many of his patients who had already failed on adapalene and tretinoin.

Using a Topical Retinoid in Combination With Other Therapies

Combination therapy is a rational approach to the treatment of any multifactorial disease as it allows the pathophysiology to be attacked from more than one angle. Such therapy offers the hope for not only improved efficacy but also a more rapid onset of efficacy. Topical retinoids are a particularly useful component of combination therapy because, by promoting comedonal drainage, they facilitate the penetration of other topical agents.

Combination therapy with an antibacterial agent

Dr Kakita reported no problems of compatibility using tazarotene in combination with azelaic acid, and Dr Webster reported no problems of compatibility using tazarotene in combination with benzoyl peroxide.

Combination therapy with an antibiotic

The combined use of a topical antibiotic (clindamycin) and a topical retinoid (tretinoin) has been shown to achieve greater and more rapid responses from inflammatory lesions than treatment with either agent alone.[24,25] For non-inflammatory lesions, such a combination has been shown to have greater efficacy than antibiotic alone, and comparable efficacy to topical retinoid alone.[24,25] There are currently no fixed combination formulations available in the United States that incorporate an antibiotic with a topical retinoid, although an erythromycin and tretinoin gel is available in Canada. Nevertheless, Dr Poulin reported that he had achieved good efficacy and tolerability using a pharmacy-prepared mixture of clindamycin powder and tazarotene gel (600 mg clindamycin powder in 30 g tazarotene gel). However, extemporaneously formulated combinations are usually unstable.

It is hypothesized (though not proven) that a topical or oral antibiotic, given early in the course of treatment, may be useful in helping to prevent a pustular flare. However, although an oral antibiotic is often used in combination with a topical retinoid, there are 2 potential problems. First, many female patients taking a contraceptive pill do not want to take oral antibiotics

because of a possible increased risk of pregnancy, even though the preponderance of evidence argues against the existence of this interaction with antibiotics commonly used for acne.[26] (Occasionally, in female patients, an antiandrogen such as cyproterone acetate—which is available in Canada combined with ethinylestradiol, but is not available in the USA—can be considered. If this is not available, spironolactone is another option in patients who are also taking a contraceptive pill. Although spironolactone may be associated with irregular menstruation and should be avoided during pregnancy, these potential problems are obviated when the patient is already taking a contraceptive pill. Both cyproterone acetate and spironolactone help to reduce the oiliness of the skin, while the topical retinoid provides the comedolytic effect). Second, rational prescribing is imperative in order to confront the problem of antibiotic resistance. The overall incidence of *P. acnes* resistance to antibiotics has increased from 20% in 1978 to 62% in 1996.[27] Resistance is most commonly reported with erythromycin and clindamycin, and is also occasionally induced by tetracycline, doxycycline, and trimethoprim. The use of benzoyl peroxide prevents the emergence of resistance. Erythromycin-benzoyl peroxide also decreases the emergence of resistance and has been shown to be better tolerated than benzoyl peroxide alone.

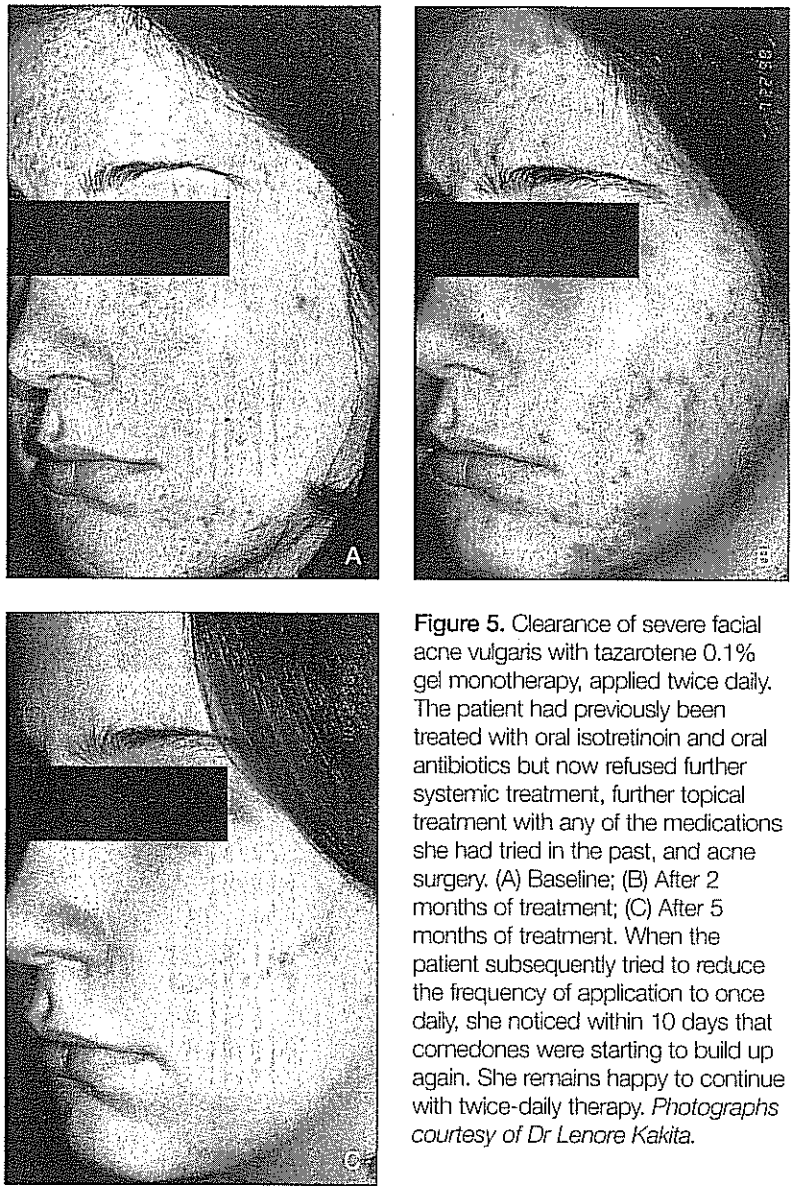

Figure 5. Clearance of severe facial acne vulgaris with tazarotene 0.1% gel monotherapy, applied twice daily. The patient had previously been treated with oral isotretinoin and oral antibiotics but now refused further systemic treatment, further topical treatment with any of the medications she had tried in the past, and acne surgery. (A) Baseline; (B) After 2 months of treatment; (C) After 5 months of treatment. When the patient subsequently tried to reduce the frequency of application to once daily, she noticed within 10 days that comedones were starting to build up again. She remains happy to continue with twice-daily therapy. *Photographs courtesy of Dr Lenore Kakita.*

Although individual patients may not suffer from antibiotic resistance, long-term use of antibiotics may contribute to the pool of resistant organisms.[28] Furthermore, sequential antibiotic therapy for acne has been shown to exert selective pressure for increased skin carriage of resistant coagulase-negative staphylococci, not only in patients but also in their close contacts.[29]

Thus, in many patients with acne, *maintenance* treatment without benzoyl peroxide or erythromycin-benzoyl peroxide, and with an oral antibiotic, is inappropriate or ineffective. It is important to recognize therapeutic failure and alter treatment accordingly. Antibiotics are not essential for the successful treatment of acne[28] and Dr Leyden emphasized that excellent improvements can be achieved with topical retinoid monotherapy (although faster improvements and better overall results are achieved using a topical retinoid in combination with an antibiotic). In mild-to-moderate facial acne, Dr Poulin reported treatment success (50% improvement or more) within 8-12 weeks using only tazarotene gel (0.05% or 0.1%) monotherapy, once daily. In severe acne, Dr Kakita reported complete clearance after 5 months of treatment with tazarotene 0.1% gel monotherapy, applied twice daily (Figure 5).

Adjunctive use of a topical corticosteroid

Most dermatologists agreed that the use of a topical corticosteroid is generally not advised in the treatment of acne. If a steroid is used to treat excessive skin irritation, great caution must be exercised to avoid the

development of steroid dependence or perioral dermatitis, which is commonly associated with long-term use. To help prevent patients from applying a steroid more often than recommended (1-3 applications only), it is helpful to give them a sample package of the steroid instead of telling them to buy it over-the-counter or giving them a prescription.

Different Approaches to Applying Topical Retinoid Therapy

As tazarotene is the most recently available topical retinoid, delegates discussed at length the different methods of application that they have developed for its use in their own practices. Although all dermatologists were in agreement that patients should be advised to ensure their faces are washed gently, using a mild, non-soap cleanser and avoiding drying products, they had different approaches to optimizing the efficacy and tolerability of treatment. Dr Kakita advises patients to apply a pea-sized amount of a non-comedogenic moisturizer directly after washing their face and then to apply a pea-sized amount of tazarotene gel after this. (Greater use of moisturizer is advised against as this will dilute the concentration of tazarotene in the gel.) Dr Kakita believes that applying tazarotene on hydrated, exfoliated skin enhances the absorption and hence maximizes efficacy without affecting tolerability. Dr Brodell takes a different approach and uses the same method he does with tretinoin—to wait 15 minutes after washing before applying tazarotene (alone, without a moisturizer). He tends to initiate tazarotene therapy using the 0.05% gel every other night, with clindamycin lotion or other topical antibiotic moisturizer in the morning. Dr Poulin takes a third approach and suggests initiating therapy using Dr Bershad's short-contact method of tazarotene application (directly after washing the face), each evening, and, if well tolerated, to progress to applying tazarotene each evening without washing it off afterwards.

Dose titration with tretinoin can be achieved by progressing from the 0.025% cream to the 0.05% cream and the 0.1% cream, or by progressing from the 0.01% gel to the 0.025% gel. Similarly, dose titration with tazarotene can be achieved by progressing from the 0.05% gel to the 0.1% gel formulation, and also by varying the frequency of application (from once every 2 or 3 days for initial therapy in the most sensitive patients, up to once daily, and, if necessary, even twice daily). If sample tubes are available, the most cost-effective way to initiate therapy with the 0.05% gel, and then progress to the 0.1% gel, is to give the patient a sample tube of the 0.05% gel together with a prescription for the 0.1% gel. As the gel should be applied sparingly, the sample lasts long enough for the skin to become acclimatized to the drug before the 0.1% gel is introduced.

Dr Kakita described how the frequency of tazarotene application in an individual patient can be optimized by monitoring the build up of comedones in that patient. If comedonal buildup continues despite once-daily treatment, she believes that it can be almost eliminated in some patients with twice-daily treatment. This opportunity to optimize therapy using twice-daily treatment may be applicable to tazarotene treatment only—with adapalene, efficacy may not be increased sufficiently and, with tretinoin, tolerability may be a limiting factor.

Suggestions for Patient Management

Typically, first-line treatment for patients presenting with mild-to-moderate acne vulgaris is likely to be a topical retinoid ± benzoyl peroxide, erythromycin-benzoyl peroxide, or a topical antibiotic. In addition, a short course of an oral antibiotic may be useful in helping to prevent a pustular flare. Patients with more severe acne are likely to be treated with a topical retinoid plus an oral antibiotic ± a topical antibacterial. Although the use of antibiotics should be tapered off as quickly as possible (tapering the oral antibiotic first and the topical antibiotic second), the retinoid may need to be continued for 1 or more years, until the acne resolves spontaneously.

Using these treatments and, if necessary, oral isotretinoin or hormonal treatment, it should be possible to achieve adequate control of all cases of acne with optimal patient compliance. To achieve this, it is important to: discuss the treatment with the patient before it is started, explain the rhythm of improvement, discuss clinical expectations (both efficacy and tolerability), advise on the concomitant use of other skin products, warn about exposure to sunlight and sunlamps, and give clear written instructions for the patient to take home.

Initial consultation

The dermatologists at the roundtable meeting agreed that the first appointment is the most important consultation. A detailed discussion with the patient at this stage will pay dividends in the future, with less risk of misunderstandings and compliance problems, and a realistic view of what they may expect from treatment. The patient needs to be informed about acne, possible treatment options and clinical expectations from each, application techniques for topical therapy (including the concomitant use of other skin products), possible tolerability problems and how to deal with them, and any cost

issues. They should also realize that acne can cause irreversible scarring and that the chances of minimizing the risk of scarring are much better when treatment is started as early as possible.[30]

Wherever possible, give patients samples to try before committing them to significant financial outlay. If it is not clear which strength of a topical retinoid formulation will be optimal for an individual patient, give them different strength samples and follow up with a prescription once it is clear which strength is optimal for that patient.

The rhythm of improvement

Patients should be advised that a small percentage of patients may experience a pustular flare, and so an *apparent* worsening of their acne, during the first few weeks of therapy and before clinical improvement becomes evident. This phenomenon, which appears to be produced by breakdown of the follicular epithelium of the microcomedo, extrusion, and subsequent inflammation of subsurface lesions, has been reported with tretinoin therapy[31] and, anecdotally, with tazarotene, adapalene, and oral isotretinoin therapy. Patients should be warned of this potential effect and reassured that it is not only transient but also an indication of the effectiveness of therapy.

Clinical expectations

Inform the patient that the expected improvement with topical retinoid therapy is achieved only after a reasonable treatment period, which is usually 4-8 weeks but may be as long as 15 weeks. Furthermore, topical acne therapy may need to be continued for a year or more, or even indefinitely, in order to sustain the improvement.[30]

Tretinoin treatment can be expected to achieve good to excellent results in 8-12 weeks. Dr Kakita's clinical experience with tazarotene suggests that relatively aggressive therapy with twice-daily applications of the 0.1% gel achieves a 70% improvement in acne lesions, especially papulopustular lesions, within 4 weeks. It is likely that almost all comedones, pustules, and cysts will clear over the course of the next 3 to 4 months. Dr Poulin's clinical experience with applying tazarotene less aggressively (once daily or once every other day), suggests that an improvement of 50% or more is often achieved within 8-12 weeks. Dr Bershad has seen dramatic results within 4 to 8 weeks of twice-daily short-contact tazarotene therapy, but noted that it is not unusual to see a more gradual improvement over 3 to 4 months of therapy.

In Dr Bershad's experience, although all the topical retinoids achieve maximum improvement within approximately 4-20 weeks, she has not seen the same degree of acne lesion reduction with tretinoin and adapalene as she has with tazarotene.

Transient local skin irritation is the most likely adverse effect of therapy with any topical retinoid. Generally, this is likely to be most noticeable in the first 2-4 weeks of therapy and to resolve thereafter even with continued topical retinoid therapy. Erythematous post-inflammatory coloration may occur during the first few weeks, but tends to diminish over the ensuing 4 to 6 months as treatment continues. The frequency of application, and the concentration of the retinoid formulation, can be adjusted if the patient finds tolerability a problem. In addition, the use of non-soap cleansers and moisturizers—with or without topical antibiotic—help to eliminate any localized areas of dryness.

Concomitant use of other skin products

Advise patients to use cosmetic products and makeup that are non-greasy and labeled as non-comedogenic.[30] When using a topical retinoid, patients should use a mild, non-abrasive cleanser and a gentle shampoo, and they should avoid the use of astringents and other drying products (eg, other retinoids, harsh soaps and gels, and salicylic acid preparations).

Exposure to sunlight and sunlamps

Tretinoin has been shown to be degraded in the presence of ultraviolet light[32] whereas, in contrast, both tazarotene[33] and adapalene[32] have been shown to be photostable. Nevertheless, because of a heightened susceptibility to burning with these retinoids (which may be attributable to a thinning of the stratum corneum), the product labeling for all 3 drugs advises patients to minimize their exposure to sunlight and sunlamps during treatment. For this reason, all patients should be advised to apply an oil-free sunblock prior to any exposure to ultraviolet light.

Written instructions

To reinforce and complement what is discussed during their consultation, most of the dermatologists at the roundtable meeting give their patients written instructions to summarize the key information they need to know. The most important topics to include in such a summary are: the correct application technique; the frequency and time of day of application; how to adjust the dose or frequency of application in response to efficacy and tolerability; the concomitant use of other skin products; the need for reliable contraception; the potential risks associated with the treatment if pregnancy

does arise; the need to stop treatment and seek medical attention if pregnancy does occur. It is particularly important to instruct patients on what to do if they experience tolerability problems so that they know how to adjust their treatment regimen successfully. This should help prevent them becoming disillusioned and discontinuing their treatment prematurely.

It is also worthwhile emphasizing to patients that they should be applying their topical acne medications to the entire area of acne-affected skin (avoiding the eye, eyelid, and mouth area), and not just spot-treating individual lesions (which would not prevent new acne lesions from developing). They should also be aware that they should wash their hands after applying any topical retinoid to avoid the risk of irritant dermatitis developing on their hands.

Follow-up

The dermatologists varied in how soon after the initial consultation they felt it was useful to see patients again. Most of them saw their patients again after 4-6 weeks, as they found it helpful to check on tolerability, application techniques, and clinical progress. However, some dermatologists waited for 3-6 months before seeing their patients again and reported no problems with this approach. It is important to remind patients that they can always call before their next visit if they need telephone advice about their treatment.

Conclusions

An overview of some of the clinically relevant characteristics of the different topical retinoids is provided in Table II. Ultimately, the choice of which topical retinoid therapy to use appears to depend on selecting the balance between efficacy and tolerability that is most suited to each patient. For patients who want the most rapid, efficacious and complete improvement, treatment with tazarotene or one of the higher concentration tretinoin formulations would be suitable, particularly in combination with an oral and/or topical antibiotic. For patients who fail with tazarotene, oral isotretinoin might be suitable. If tolerability is an issue, adapalene or one of the lower concentration tretinoin formulations would be suitable, combined with an oral and/or topical antibiotic.

Table II

COMPARATIVE EVALUATION OF CLINICALLY RELEVANT CHARACTERISTICS OF THE AVAILABLE TOPICAL RETINOIDS

	Tretinoin	Adapalene	Tazarotene
Suitable for first-line therapy	Yes	Yes	Yes
Treatment option in refractory patients	Yes	—	Yes
Used successfully in severe acne	Yes	—	Yes
Can be tolerated in type 1 skin	Yes	Yes	Yes
Photostable	—	Yes	Yes

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