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The Rationale for Using a Topical Retinoid for Inflammatory Acne

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Abstract

Both comedogenesis and the development of inflammatory lesions in acne vulgaris appear to be related to genetic as well as immune processes. The key regulatory cytokine, interleukin-1α, has recently been documented as playing a major role in both the hypercornification and the orchestration of immune factors, ultimately resulting in noninflammatory and inflammatory lesions. Topical retinoids, such as tretinoin, and topical retinoid analogs, such as adapalene and tazarotene, help normalize the abnormal follicular keratinocyte desquamation – a key pathophysiologic factor in comedogenesis. This normalization also helps mitigate against the development of a propitious microenvironment for *Propionibacterium acnes*. Preclinical data suggest that topical retinoids and retinoid analogs may also have direct anti-inflammatory effects. A wealth of clinical data confirms that topical retinoids and retinoid analogs significantly reduce inflammatory lesions. Comparative clinical trials also demonstrate that adapalene has the best cutaneous tolerability profile of all these agents. Optimal therapy for inflammatory acne would involve the use of topical retinoids or retinoid analogs combined with oral or topical antibacterials.

1. The Pathophysiology of Inflammatory Acne

The clinical mantra for explaining the pathophysiology of acne vulgaris lists four events: (i) abnormal follicular keratinocyte desquamation leading to the formation of a follicle plug; (ii) increased sebum production within the pilosebaceous follicle; (iii) proliferation of the microorganism *Propionibacterium acnes* in the sebum; and (iv) inflammation.[1-3] Although it is generally agreed that acne vulgaris involves a multifactorial etiology, the relative importance of each etiologic factor and the pathogenic sequence of events relating to the various stages of acne are just being elucidated. For instance, it is now recognized that comedogenesis can occur independent of *P. acnes* colonization in the follicle.[4,5]

Interest in the role of the immune system in acne is supported by new studies.[6-8] *In vitro* studies have demonstrated that the cytokine interleukin-1α, derived from ductal keratinocytes, can promote hypercornification in the absence of other mediators.[5,6] The addition of an interleukin-1α receptor antagonist to experimental acne systems can inhibit the growth of comedones.[5,9]

Although most researchers believe that inflammatory acne lesions develop from microcomedones, the process by which this occurs has not been definitively established. Kligman[10] suggested in the 1970s that the initial inflammatory event in acne vulgaris involves the disruption of the follicular epithelium into the dermis, allowing the pro-inflammatory and immunogenic comedonal contents to have contact with the vascular and inflammatory systems. Recently, Eady and Cove[6] suggested that permeability changes in the follicle wall, rather than actual rupture, could allow the movement of cytokines, including ductal interleukin-1α, into the dermis. Ingham and colleagues[11] biopsied open comedones from 18 patients with untreated acne and found the presence of a bioactive interleukin-1α–like substance in 76% of open comedones. They suggested that this cytokine might be involved in the initiation of inflammatory acne lesions.

Kligman also suggested that neutrophils constitute the initial cellular infiltrate in inflammatory lesions.[10] However, more recent histologic studies of early events in acne inflammation using timed biopsies have demonstrated that lymphocytes constitute the initial cellular infiltrate.[12,13] Other cells involved in inflammation (e.g. neutrophils, monocytes/macrophages) then follow.

The follicular plugs and sebum accumulation are propitious to the growth of *P. acnes*. Eady and Cove[6] maintain that *P. acnes* and products in the blocked follicles are responsible for maintaining and augmenting ongoing inflammation.

Thus, all four pathogenic factors – abnormal keratinization, excessive sebum production, *P. acnes* colonization, and inflammation – play a role in the process. Agents (or a combination of

agents) that address multiple pathophysiologic factors would logically be the most effective approach for the treatment of patients with inflammatory acne (table I).

2. Therapies for Inflammatory Acne

Topical therapy with retinoids, benzoyl peroxide, or antibacterials continues to be the initial step for both males and females. Oral antibacterials are seen as the next step in therapy, and the final step, for severe forms of acne vulgaris, is the use of systemic retinoids such as isotretinoin (table II).[15] Many of these interventions are thought to have immunomodulatory effects. Hormonal therapy is beginning a resurgence in acne therapy and may play an additional anti-inflammatory role.[16]

2.1 Retinoids and Retinoid Analogs

Retinoids and retinoid analogs normalize the hyperkeratinization process, ameliorating follicular blockage and the resulting initiation or augmentation of the inflammatory process. Experimental evidence suggests that they may exert direct immunomodulating actions as well.

It is well established that retinoids (e.g. tretinoin, isotretinoin) and retinoid analogs (e.g. adapalene, tazarotene) modulate growth and differentiation of the epidermis. They induce epidermal proliferation in normal skin, but help normalize growth and differentiation of epithelia that are already hyperproliferative.[17] Retinoids and retinoid analogs may exert their antiproliferative effect by modulating various cell growth factors.[18] Both tretinoin and adapalene have been found to inhibit the expression of the keratinocyte enzyme transglutaminase.[19] This enzyme is responsible for facilitating cross-links between keratin proteins,

Table I. Topical therapies available for the treatment of acne and their impact on etiologic factors (reproduced from Layton,[14] with permission)

Topical therapy	Inflammation	Comedogenesis	Reduction in *Propionibacterium acnes*
Benzoyl peroxide	+[a]	+	++
Retinoids			
Tretinoin	+	++	–
Isotretinoin	+	++	–
Adapalene	+	++	–
Antibacterials			
Erythromycin	++	+/–	+
Tetracycline	++	+/–	+
Clindamycin	++	+/–	+

a Benzoyl peroxide has an indirect action on inflammation.
– indicates no effect; + indicates mild effect; ++ indicates strong effect.

Table II. Treatment algorithm for acne vulgaris[15]

Disease severity	Treatment options
Grade I (mild)	Topical retinoids
	Benzoyl peroxide or topical antibacterials
Grade II-III (moderate)	Topical retinoids
	Benzoyl peroxide or topical antibacterials
	Oral antibacterials
	Hormone therapy (females only)
Grade IV (severe)	Isotretinoin or, for females only, topical retinoids, oral antibacterials, and hormonal therapy
Maintenance	Topical retinoids ± benzoyl peroxide

causing a cohesiveness that, in turn, results in the keratin plug. These actions of retinoids and retinoid analogs are thought to result in reduced proliferation and cohesion of the cornified cells in the infundibulum, the part of the follicular canal closest to the sebaceous gland. Ultimately, this results in a shedding of the comedone and enhanced drainage from the follicular lumen.

Anti-inflammatory effects may also account for the efficacy of retinoids and retinoid analogs in treating the inflammatory lesions in patients with acne vulgaris.

2.2 Antimicrobials – Antibacterials and Benzoyl Peroxide

Antibacterials are effective in the treatment of inflammatory lesions. Antibacterial-mediated improvement of these lesions appears to be a result of the reduction in *P. acnes* population as well as a modulation of the pathogen-induced inflammatory effects. Webster and colleagues[20,21] demonstrated that concentrations of tetracycline and erythromycin small enough to have no effect on pathogen growth or viability nevertheless decreased the production of certain degradative enzymes (lipases) and chemotactic factors released by *P. acnes*. Some antibacterials, such as erythromycin, tetracyclines, and clindamycin, may also have direct anti-inflammatory activity, independent of their effects on *P. acnes*.[22,23] The antimicrobial agent benzoyl peroxide appears to inhibit a key signaling pathway in neutrophils, compromising their inflammatory actions, including the release of reactive oxygen species.[24]

3. Clinical Trials of Retinoids

3.1 Experimental Evidence for Anti-Inflammatory Effects

The anti-inflammatory effects of tretinoin have been demonstrated in in vitro studies.[25,26] In these studies, tretinoin inhibited the release of various proinflammatory cytokines, such as interleukin-6 and interferon-γ.[25] In another *in vitro* study, both

tretinoin and isotretinoin were found to modulate the function of macrophages,[26] key inflammatory cells that engage in phagocytosis of antigenic material and pathogens. The retinoids caused a greater than twofold increase in phagocytosis by the mouse macrophage cell line, RAW.

Leukotrienes are products of the lipoxygenase pathway of arachidonic acid metabolism and these key inflammatory mediators are thought to be operative in acne vulgaris. Adapalene demonstrated greater inhibition of the lipoxygenase pathways and leukotriene production *in vitro* compared with three retinoids (tretinoin, isotretinoin, etretinate), indomethacin, and betamethasone-17-valerate.[27] While adapalene and tretinoin both exhibit comparable inhibition of the release of oxygen-free radicals from rabbit neutrophils, animal models have suggested that adapalene provided greater *in vivo* ability than tretinoin to reduce experimentally induced edema and erythema.[27] An oral 5-lipoxygenase inhibitor, currently being evaluated in clinical trials in Europe for the treatment of patients with acne vulgaris, resulted in significant reductions in inflammatory lesions.[8]

A recent study of retinoids demonstrated their ability to inhibit the expression of mammalian toll-like receptors from normal human monocytes *in vitro*.[28] Toll-like receptors are members of the interleukin-1 receptor family and are expressed by a number of immune cells. Activation of these receptors by microbial pathogens can trigger intracellular pathways that lead to the release of various pro-inflammatory cytokines.[29] When adapalene was cultured with monocytes, the expression of toll-like receptor 2 was inhibited by approximately 80%.[28] Retinoic acid similarly inhibited the expression of toll-like receptor 2.[28]

Both adapalene and tretinoin inhibit the expression of the transcription factor AP-1, an important regulator of the expression of growth factors (e.g. vascular endothelial growth factor) and degradative enzymes (e.g. matrix metalloproteinases) involved in inflammatory responses.[30] In experimental models of psoriasis, tazarotene demonstrated modulation of T cells and AP-1.[31] A summary of the proposed immunomodulatory effects of retinoids is presented in table III.

3.2 Effects on Inflammatory Lesions

Based on their mechanisms of actions, topical retinoids would be expected to effectively reduce inflammatory lesions. Various formulations of adapalene (gel, cream, solution), tretinoin (gel, microsphere gel, cream), and tazarotene gel have all been found to significantly reduce inflammatory lesions in well-controlled clinical trials.[32-41] Most comparative studies of these various retinoid agents demonstrated comparable efficacy, with some exceptions. In a randomized, investigator-blinded study of 105 patients, adapalene 0.1% gel was significantly more effective in reducing inflammatory lesions compared with tretinoin 0.025% gel (33 vs 17% reduction, $p = 0.001$).[33] In a multicenter, double-blind, randomized, parallel-group trial, tazarotene 0.1% gel was found to be more effective than adapalene 0.1% gel in reducing the median number of inflammatory lesions ($p = 0.0002$); although notably, patients rated both treatments equally effective. Perhaps of greater clinical relevance was the observation that tazarotene was associated with significantly greater skin irritation than adapalene ($p < 0.01$).[42]

3.2.1 Onset of Action

The comparative onset of action of these agents is somewhat controversial. In one double-blind, 12-week trial, tretinoin 0.1% microsphere gel demonstrated a greater reduction in comedone counts at week 4 compared with adapalene 0.1% gel ($p = 0.047$), although similar reductions using either agent were observed at weeks 1–3; reduction in total lesion counts at week 12 were also similar.[43] In contrast, a meta-analysis of five multicenter, randomized, investigator-blinded trials found that adapalene 0.1% gel exerted more rapid effects compared with tretinoin 0.025% gel as evidenced by a significantly greater reduction in inflammatory lesions during the first week of treatment[40] (see table IV for onset of action data for one of the studies included in the meta-analysis).[33,41]

3.3 Cutaneous Tolerability of Topical Retinoids

Retinoid dermatitis, especially with earlier formulations of tretinoin, often made treatment of inflammatory lesions with top-

Table III. Proposed immunomodulatory effects of adapalene, tretinoin, and tazarotene[25-28,30]

Retinoid/retinoid analog	Symptoms of inflammation (e.g. edema, erythema)	Cellular basis of immunomodulatory effects (e.g. inhibition of inflammatory mediators, modulation of leukocyte accumulation)	Molecular basis of immunomodulatory effects (e.g. inhibition of TLR expression, AP-1)
Adapalene	++	++	++
Tretinoin	+	+	++
Tazarotene		++	++

AP-1 = transcription factor AP-1; **TLR** = toll-like receptor; + indicates relatively less inhibition or less support from preclinical data; ++ indicates greater inhibition or greater support from preclinical data.

Table IV. Onset of action of adapalene gel 0.1% versus tretinoin gel 0.025% as evidenced by reduction of acne lesions and reduction in global severity of acne after 1 week of treatment[33,41]

Outcomes	Reduction (%) using	
	adapalene gel (n = 52)	tretinoin gel (n = 53)
Total lesions	28	22
Inflammatory lesions	32	17
Global severity	27	16

ical retinoids problematic. Significant erythema, burning, cracking and peeling of the skin – as well as an initial flare-up of lesions – often compromise patient compliance.[16] Despite the advent of more tolerable retinoid analogs, such as adapalene and newer formulations of tretinoin designed to minimize skin irritation, topical retinoids are still perceived to cause severe irritation, and hence, are underused for inflammatory acne in Europe[16] and the United States.[44]

Adapalene has, on balance, demonstrated the best tolerability profile of all topical retinoids and retinoid analogs.[32,40,41] The superior tolerability of adapalene was demonstrated in a recent 21-day cumulative irritation study comparing adapalene (gel and solution formulations) with newer retinoid and retinoid analog formulations: tretinoin 0.025% gel and cream (Avita®[1]), tretinoin 0.1% microsphere (Retin-A Micro®), and tazarotene 0.05% and 0.1% gel (Tazorac®). The test drugs were applied to the patients' backs in four 24-hour applications and one 72-hour application weekly for 3 weeks. Each application involved approximately 50ml under occlusion. Tolerability was measured by the mean cumulative irritancy index. This index was derived from the sum of erythema scores/number of readings. Erythema was graded on a 5-point scale. Adapalene was found to be the product least likely to cause skin irritation[41] (table V). A possible shortcoming of this study is that it is a summary of several trials.

A recent split-face tolerability study found somewhat conflicting results. This study demonstrated that tazarotene 0.1% gel applied every other day was associated with comparable efficacy and tolerability to adapalene 0.1% gel applied daily.[45] However, the alternate day treatment regimen with tazarotene resulted in less drug exposure. Results of this study must be considered in the context of substantial clinical data that repeatedly demonstrate the superior tolerability of adapalene. Better tolerability of a topical retinoid may have important clinical implications (e.g. compliance).

1 Use of tradenames is for product identification only and does not imply endorsement.

3.4 Topical Retinoids in Combination with Antibacterials for Treatment of Inflammatory Lesions

The combination of topical retinoids or retinoid analogs with oral or topical antimicrobials arguably constitutes the optimal treatment approach for patients with inflammatory acne. This combination addresses three of the pathophysiologic factors involved in inflammatory acne: ductal hypercornification, *P. acnes* proliferation, and inflammation. Furthermore, topical retinoids and retinoid analogs can facilitate follicular penetration of topical antibacterials and benzoyl peroxide.[46] Use of topical retinoids concomitantly with antibacterials can also reduce antibacterial exposure, thus decreasing the risk of bacterial resistance. The most compelling reason for use of this treatment approach is its ability to provide additive and accelerated effects in reducing inflammatory lesions.

A number of studies have demonstrated the benefits of combination therapy involving topical or oral antibacterial therapy and retinoids or retinoid analogs.[47-50]

The fixed combination of clindamycin phosphate 1% and tretinoin 0.025% gel was associated with a significantly greater reduction in noninflammatory lesions ($p = 0.05$) and inflammatory lesions ($p = 0.018$) compared with the clindamycin 1% lotion alone after 12 weeks of therapy. In addition, the combination therapy resulted in an accelerated improvement, especially of open comedones, compared with clindamycin alone.[48]

A 12-week randomized, multicenter trial involving 249 patients with mild-to-moderate acne assessed the effects of dual therapy involving adapalene gel 0.1% plus clindamycin 1% compared with a clindamycin plus vehicle regimen. The combination therapy regimen resulted in significantly greater reduction in inflammatory lesions ($p = 0.004$) and noninflammatory lesions ($p < 0.001$) compared with clindamycin monotherapy at 12 weeks. The combination regimen also resulted in accelerated improvement of lesions. Adverse events were similar in the combination group and the clindamycin monotherapy group.[49]

In a study evaluating adapalene gel 0.1% plus oral lymecycline 300 mg/day in 118 patients with moderate inflammatory acne,

Table V. Cutaneous tolerability of various drugs[41]

Drug (tradename)	Strength (%)	Formulation	Mean irritation index
Adapalene (Differin®)	0.1	Solution	0.05
Adapalene (Differin®)	0.1	Gel	0.06
Petrolatum			0.02
Tazarotene (Tazorac®)	0.05	Gel	1.69
Tazarotene (Tazorac®)	0.1	Gel	1.81
Tretinoin (Avita®)	0.025	Gel	0.18
Tretinoin (Avita®)	0.025	Cream	0.48
Tretinoin (Retin-A Micro®)	0.1	Gel	0.63

the combination therapy was significantly more effective than the oral antibacterial alone in reducing both noninflammatory and inflammatory lesions ($p = 0.0519$ and $p = 0.0001$, respectively).[50]

4. Conclusion

Suboptimal treatment of inflammatory acne can result in problematic sequelae. The roles of inflammation and inflammatory mediators in acne are more clearly elucidated and offer a rationale for the broader use of topical retinoids in treating patients with inflammatory acne. *In vitro* and clinical data confirm that topical retinoids and retinoid analogs address key pathophysiologic factors leading to the development of inflammatory lesions, since they significantly reduce the incidence of these lesions in patients. Some data exist that suggest adapalene may have a more rapid onset of action, though conflicting reports for tretinoin have been made. There is a preponderance of clinical evidence, however, to support the superior tolerability of adapalene. In the context of what may be comparable efficacy among topical retinoids, better tolerability may have important clinical implications in 'real-world' settings, such as for patient compliance.

Combination therapy with topical retinoids or retinoid analogs and oral or topical antibacterials addresses three out of four of the pathophysiologic factors that initiate and sustain inflammatory lesions. Recent clinical data suggest that this combination regimen is optimal for the management of inflammatory acne.

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