IAA Consensus Document

Topical retinoids

Retinoic acid, the progenitor of retinoids, was tested in 1960's by Gunter Stüttgen and Rudolf Baer who discovered its beneficial effects in disorders of keratinization.[1] Subsequently, retinoids have been found to be very useful in the treatment of acne, especially as they affect both keratinocytes and sebocytes. Topical retinoids act primarily on the keratinocytes and they do so by binding with specific receptors in the nucleus.[2] There are two types of receptors – retinoic acid receptors (RAR's) and retinoic X receptors (RXR's), each of which has three subtypes: alpha, beta, and gamma. RAR gamma is the most ubiquitous RAR in the human skin and is thought to be the main mediator of retinoid effects on keratinocytes. Adapalene and tazarotene are receptor selective retinoids, whereas tretinoin and isotretinoin are nonselective.[2]

Topical retinoids play a vital role in the treatment of mild to moderate acne through multiple actions. They act on the primary lesion – the microcomedo.[3] By regulating the rate of differentiation and proliferation of the follicular keratinocytes, they inhibit the formation of and reduce the number of microcomedones. Topical retinoids promote normal follicular keratinocyte desquamation and thus help mitigate against the development of a propitious microenvironment for *P. acnes*.[4] Some topical retinoids, namely, adapalene and tazarotene, have anti-inflammatory activity.[3] Both adapalene and tretinoin inhibit the expression of transcription factor activator protein (AP-1), an important regulator of the expression of growth factors (i.e., vascular endothelial growth factor) and degradative enzymes (matrix metalloproteinases-MMPs) involved in inflammatory responses.[5] They thin the stratum corneum by decreasing the number of cell layers, thereby potentiating the penetration of topical agents, but this also leads to increased sensitivity to sun.[6]

TOPICAL RETINOIDS HAVE MULTIPLE ANTIACNE ACTIONS

- They inhibit the formation of and reduce the number of microcomedones.
- Reduce the number of mature comedones.
- Reduce inflammatory lesions.
- Promote normal desquamation of follicular epithelium.
- Some are anti-inflammatory.
- Likely to enhance penetration of other drugs.
- Likely to maintain remission by inhibiting microcomedo formation.

At the molecular level, topically applied retinoids are taken up by the keratinocytes where they transcribe after binding to the receptor sites. This results in activation or inhibition of certain steps in gene transcription which affects keratinocyte proliferation and/or differentiation and with some retinoids, inflammation.[1] Topical retinoids inhibit the production of keratohyaline granules by follicular keratinocytes and this in turn inhibits the comedone formation.[1] Topical retinoids modulate in vitro macroaggregation of keratin filaments and thus decreasing the coherence of keratinocytes in the comedone.[1] Some retinoids such as tretinoin increase the mitotic activity of the ductal keratinocytes, leading to increased turnover of the infundibular keratinocytes and accelerated protrusion of the comedone.[1]

The currently available topical retinoids for acne, internationally, include tretinoin, adapalene, tazarotene, isotretinoin, motretinide, retinaldehyde, and retinoyl β-glucuronide.[7] Tretinoin, adapalene, and tazarotene are approved by the US FDA and have favorable safety profiles. In India, tretinoin (0.025%, 0.05%, 0.1%, as cream, gel, and solution), adapalene (0.1% gel), tazarotene (0.05% gel, 0.1% cream), and isotretinoin (0.05% gel) are available, and most are generic. Internationally, tretinoin, the oldest topical retinoid, has been reformulated as tretinoin microsphere 0.1% gel, which contains tretinoin trapped within porous copolymer microspheres; these particles selectively localize to the follicle where the drug is released over time, reducing the concentration and thus irritation.[7] Another reformulation of tretinoin (0.025% cream, 0.025% gel) utilizes a novel vehicle – polyolprepolymer 2 – designed to release tretinoin in a slow controlled manner.[7] Retinaldehyde, another molecule currently not available in India, is transformed into all-trans-retinoic acid and induces biologic effects similar to topical retinoic acid but at a lower concentration.[7] Retinaldehyde 0.1% plus 10% glycolic acid is a combination that is proving to be effective in treatment of melasma. Retinoyl β-glucuronide, a metabolite of retinoic acid, although commercially not available, was tested in India:

0.16% cream was evaluated in a vehicle controlled study over 18 weeks; significantly greater reduction in lesion counts was observed versus vehicle among 39 patients. Retinoyl β-glucuronide is water soluble and was well tolerated in this study.[8]

Although different topical retinoids have different chemical structure, they are all comedo-suppressive and target the microcomedo. There are, however, differences in efficacy and tolerability [Tables 7 and 8]. The countless clinical studies conducted till date have generated voluminous literature. There are agreements and disagreements between various studies, and at least some of the latter may be on account of differences in study design and the degree of controls. Reading through this literature one gains an impression that tazarotene is the most effective topical retinoid in acne but is also the most irritating. Adapalene, on the other hand, is least irritating and the best tolerated. Tretinoin falls in the middle of the efficacy and tolerability scale. At a more practical level, the way topical retinoids are formulated, they show comparable efficacy. For example, a meta-analysis of five large multicenter controlled studies involving over 900 patients showed that adapalene 0.1% gel was as effective as tretinoin 0.025% gel.[9] Topical isotretinoin is also comparable to tretinoin in efficacy but has no effect on the sebaceous gland. The subject of topical retinoids is well-reviewed elsewhere.[7]

Contrary to earlier belief, Indians are more sensitive and less tolerant of topical retinoids than other ethnic groups. In a study conducted at the National Skin Center, Singapore, tolerance to topical retinoids was compared between Chinese, Indians, Malays, and Europeans. It was discovered that the Indian and the Chinese women were more intolerant and experienced more subjective symptoms such as itching and burning.[10] This fits in well with the collective experience of the IAA members and additional corroboration comes from the market data. Topical retinoids, prior to introduction of adapalene, were not very popular in the treatment of acne in our country, presumably because of the irritation. Even with adapalene, we frequently encounter irritation (retinoid dermatitis); however, through gradual understanding of the pharmacology of the topical retinoids and through better patient education, it has been possible to overcome intolerance in the vast majority.

The correct methodology is the key to success and needs to be optimized. Because of photosensitivity concerns, topical retinoids are best applied at night and on the entire susceptible area. Face, which is the part treated most commonly, should be cleansed suitably (preferably with a gentle cleanser), and dried well (applying topical retinoid on wet skin is more likely to cause irritation). The quantity of cream is critical and should be such that it provides a thin layer covering the face (avoiding periorbital, paranasal, and perioral areas), and absorbs readily with gentle rubbing in 30–60 seconds. It helps to stretch the skin slightly while applying the retinoid. A safe practice is to commence with short contact, that is, to wash off the cream after a short period, say, 15 minutes. This contact time can be steadily increased to 30 minutes or so, and thereafter the cream can be left overnight. Such an approach requires giving detailed and precise instructions to the patient and this process can be standardized and made more efficient with printed hand-outs. Reduction in the frequency of application, say, to alternate nights, may also help. In

RECOMMENDED METHODOLOGY FOR TOPICAL RETINOID APPLICATION

- To avoid photosensitivity reaction, retinoids should be applied at night.
- Area to be treated (e.g., face) should be suitably cleansed and well-dried.
- As some patients are likely to react to topical retinoids the therapy should begin with short contact.
- Gradually escalating regimen – beginning with 15 minutes application, and/ or alternate night application – is best individualized.
- Controlled quantity of topical retinoid – typically a blob the size of a pea – is first dabbed (on cheeks, forehead, nose, and chin) – then gently rubbed to achieve absorption. Avoid nasal folds, periorbital, and perioral areas.
- Best therapeutic results are achieved when daily overnight application is established.
- Avoid concomitant use of other irritating topical agents.
- Avoid excessive cleansing and use of astringents.
- Retinoid dermatitis (irritant contact dermatitis) is indicative of overdose effect and is best managed by suspending treatment for 3–5 days and applying moisturizer or a topical calcineurin inhibitor. Low potency topical steroid may be used as a last resort.

Table 7: Efficacy of topical retinoids in acne[12]

Agent	Comedolytic	Sebosuppressive	Antimicrobial	Anti-inflammatory
Adapalene	++	–	–	+
Tazarotene	++	–	–	±
Tretinoin	++	–	–	-
Isotretinoin	++	–	–	±

Evidence: +++ very strong, ++ strong, + Moderate, ± weak, – none

Table 8: Cutaneous tolerability of topical retinoids[12]

Agent	Erythema	Scaling	Burning	Flare
Adapalene	+	+	+	+
Tazarotene	++	+	+	+
Tretinoin*	+++	+++	++	++
Isotretinoin	++	++	+	+

*Depends on formulation. Tolerability reactions may vary according to skin type and individual sensitivity

spite of due precautions, retinoid dermatitis (irritant contact dermatitis) is encountered in more than 50% of our patients and leads to anxiety, frustration, and even prejudice. Many patients need to be coaxed in to resuming topical retinoids. Retinoid dermatitis is easily managed by suspending the treatment for 3–5 days, and applying emollients. In more severe cases, topical pimecrolimus is useful.

Maintenance therapy with topical retinoids: The cessation of topical retinoids is known to be followed by an increase in the number of microcomedones.[11] This makes a good case for continuing topical retinoids beyond clinical clearance of acne. The duration of such maintenance therapy should be determined by the age of the patient and the anticipated remaining years of the acne susceptibility period. A reasonable generalization is to continue topical retinoids till the age of 25 years. There is, however, room for improvisation and individualizing both in terms of duration of maintenance therapy and frequency of topical retinoid application.

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