ROLE OF TOPICAL RETINOIDS IN ACNE MANAGEMENT

Topical retinoids are important tools in the management of acne because they act against comedones and micro-comedones and have direct anti-inflammatory effects.

The substances approved for acne treatment comprise tretinoin (*all-trans-retinoic acid*), isotretinoin (13-*cis* retinoic acid) as well as the synthetic third-generation polyaromatic retinoids adapalene and tazarotene, the latter being approved for acne treatment in the US only. Retinaldehyde is used in cosmetic preparations against acne.

All topical retinoids are effective as single agents in mild to moderate acne but differ in efficacy and tolerability. Tazarotene 0.1% is more effective than tretinoin 0.025% or 0.1% microsphere gel or adapalene 0.1% gel or cream.

Adapalene 0.1% is equally effective to tretinoin 0.025% or tretinoin microsphere 0.1% gel or tretinoin 0.05% cream or isotretinoin 0.05% gel. Adapalene 0.1% gel is significantly better tolerated than tazarotene 0.1% gel, tretinoin 0.025% and tretinoin 0.05% gel, tretinoin 0.05% cream, tretinoin microsphere 0.1% gel or isotretinoin 0.05% gel.

The safety profile of topical retinoids differs from their systemic counterparts and is related mainly to local adverse effects, such as erythema, dry-ness, itching and stinging. The currently available evidence justifies the use of topical retinoids in most types of acne and during maintenance treatment. [1]

MECHANISM OF ACTION OF RETINOIDS:

The biological effects of topical retinoids are mediated and regulated by nuclear hormone receptors and cytosolic binding proteins. To date, a retinoid is defined as a molecule that binds to and activates retinoic acid receptors either directly or by metabolic conversion and thereby elicits transcription of retinoic acid-responsive genes.

Retinoids influence proliferation and differentiation of cells and reverse the abnormal desquamation by increasing the follicular epithelial turnover and accelerating the shedding of corneocytes, which leads to an

expulsion of mature comedones and suppression of micro-comedone formation.

The change of the "follicular milieu" of the sebaceous gland apparatus by restoration of normal cornification promotes an inhospitable aerobic environment for *Propionibacterium acnes* and is likely to enhance the penetration of other topical drugs.

A specific direct antibacterial effect against *P. acnes* has been shown for retinaldehyde only. [2]

TRETINOIN MONOTHERAPY:

Tretinoin was first used in the early sixties by Stüttgen and Beer. Its clinical efficacy was shown as a single-agent therapy in patients with mild-to-moderate comedonal or inflammatory acne.

In a recently published bioequivalence study, two different preparations of tretinoin, Tretin-X (Triax Pharmaceuticals, Cranford, NJ) and Retin-A (Johnson & Johnson, New Brunswick, NJ) at different formulations and concentrations were efficient in mild to severe inflammatory acne compared to placebo.

Furthermore, tretinoin is effective against micro-comedones with a significant reduction of 50 % after 6 weeks and 80 % after 12 weeks of treatment with 0.1 % tretinoin cream.

Tretinoin is available as gel (0.01 % and 0.025 %), cream (0.025 %, 0.05 %, 0.1 % and 0.4 %), liquid (0.025 %, 0.5 % and 0.1 %), lotion (0.1 %), ointment (0.05 %), compresses (0.05 %), gel microsphere (0.04 % and 0.1 %) and polymer cream (0.025 %). New preparations with improved cutaneous tolerability were developed including tretinoin trapped with co-polymer microspheres (Retin-A Micro®gel, Ortho-Neutrogena, USA) or prepolyolprepolymer-2 gel or cream (Avita®, Bertek pharmaceuticals, USA), which gradually release the active ingredient over time.

Tretinoin 0.025 % gel containing poly-olprepolymer-2 demonstrated comparable efficacy to a conventional gel but significantly less peeling and dryness and was comparable to a commercially available tretinoin 0.025 % cream in terms of efficacy and safety. [3]

TRETINOIN COMBINATION THERAPY:

An early trial in 1978 reported that a twice daily application of 2 % erythro-mycin base in hydroalcoholic solution accompanied by once daily use of 0.05 % tretinoin solution was substantially more effective than monotherapy for treatment of moderate inflammatory acne.

Later on, the high efficacy and tolerability of a fixed gel preparation with 0.025 % tretinoin and 4 % erythromycin was confirmed in an open multicenter study.

A combined alcoholic erythromycin/tretinoin solution showed good efficacy and tolerability in a multicenter data investigation.

In a comparative study, 3 % erythromycin/5 % benzoyl peroxide provided significantly greater reduction in both physician-and patient-rated severity of acne symptoms and better tolerability than 0.025 % tretinoin/erythromycin 4 % after two weeks of treatment. [(3)]

The improved efficacy of tretinoin 0.05 % in combination with benzoyl peroxide (BPO) compared to either ingredient alone has been demonstrated. Both substances must be applied alternately to avoid oxidative degradation of tretinoin. Tretinoin microsphere gel showed improved stability towards UV-and oxidative-induced degradation.

Its combination with a BPO 6 % cleanser resulted in a greater reduction of inflammatory acne lesions than the monotherapy with 0.1 % tretinoin microsphere without increased skin irritation.

The combination of clindamycin phosphate1 % and tretinoin 0.025 % gel was well tolerated and significantly more effective than clindamycin 1 % or tretinoin, which was confirmed in another study investigating the effect of a clindamycin 1 %/tretinoin 0,025 % hydrogel.

A greater efficacy compared to its single ingredients was also found for a fixed combination of clindamycin phosphate 1.2 % and tretinoin 0.025 % gel (Ziana®, Medicis, USA).

A combination of clindamycin and benzoylperoxide with tretinoin was reported to be well tolerated and show improved efficacy as compared to tretinoin combined with clindamycin, however, the addition of tretinoin

to the combination of clindamycin and BPO had no additional benefit in terms of efficacy. [3]

ISOTRETINOIN:

Isotretinoin is the 13-*cis* isomer of tretinoin and is available in topical formulations (0.05 % gel or cream, 0.1 % cream). Topical isotretinoin was effective compared to its vehicle in 268 patients with mild to moderate acne.

In comparative trials, isotretinoin gel 0.05 % was equally effective to tretinoin cream 0.05 % and comparably effective to adapalene gel 0.1 %.

Isotretinoin 0.05 % was less effective against inflammatory lesions than benzoyl peroxide 5 % gel in a vehicle-controlled double-blind study. A study including 160 patients with mild to moderate acne revealed that a fixed combination of isotretinoin 0.05% and erythromycin 2% (Isotrexin®) was significantly better than placebo at all time points for inflamed and total lesions and then isotretinoin alone in the reduction of inflammatory lesions at week 4.

Isotretinoin 0.1 %/erythromycin 4 % gel given only once daily demonstrated comparable efficacy with benzoyl peroxide 5 %/erythromycin 3 % given twice daily in the treatment of mild to moderate acne vulgaris. [3]

ROLE OF RETINOIDS IN ACNE MANAGEMENT:

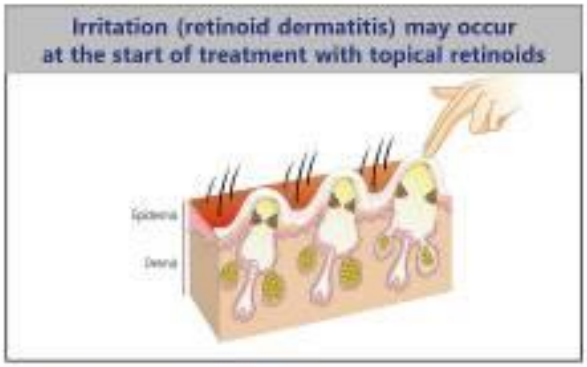
It is generally agreed that multiple molecular pathways are involved in acne, with four primary pathophysiologic mechanisms.

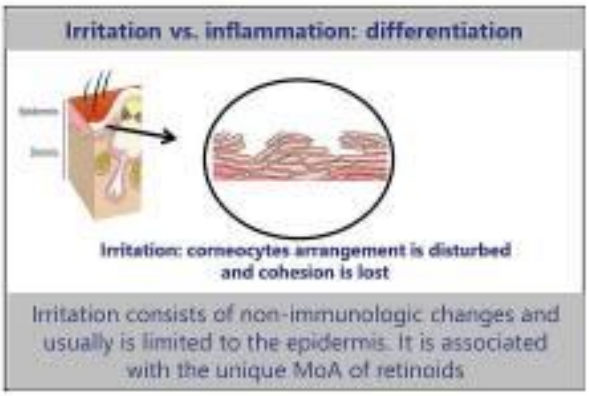
- Abnormal desquamation within the sebaceous follicles that leads to obstruction of the pilosebaceous canal.
- Androgen-driven excess sebum production.
- Proliferation within the follicle by *Propionibacterium acnes*, which generates proinflammatory stimuli.
- Altered immune system activity and inflammation. [4]

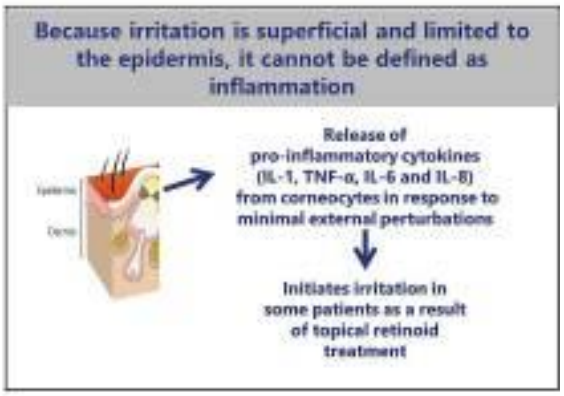
TOLERABILITY OF TOPICAL RETINOIDS:

A

Week 1

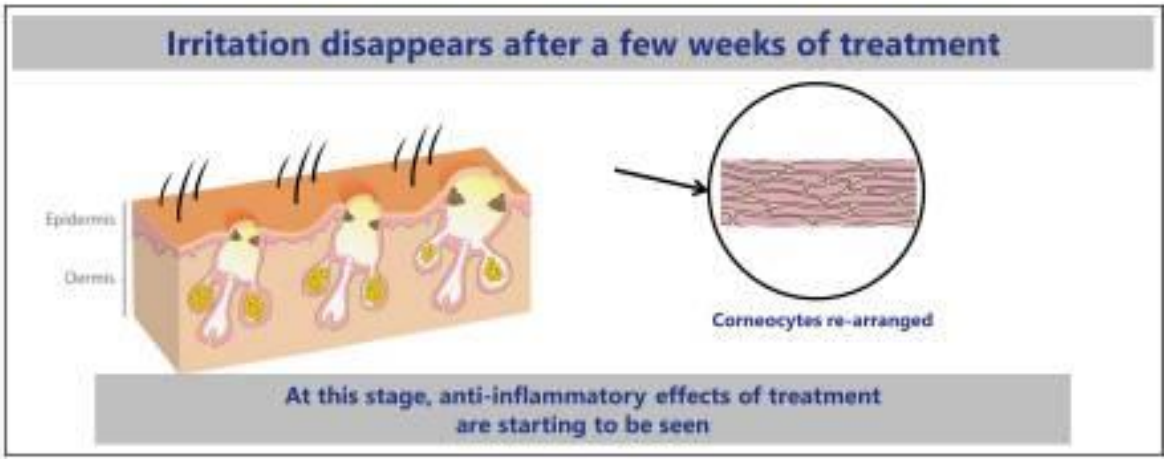






B

Weeks 2-4



STRATEGIES TO MINIMIZE TOLERABILITY ISSUES:

- Take a detailed patient history
- Past tolerability problems?
- Educate patient
- Mild irritation can be part of the treatment process, but usually subsides within 1–2 weeks and can be managed with appropriate steps
- How to apply the retinoid in a thin layer (fingertip or pea-sized dose)
- Gentle cleansing regimen and avoiding over-cleansing
- Select most tolerable retinoid formulation for climate and season
- Titrate retinoid dose at initiation
- Apply retinoid every other day for first 2–4 weeks (based on clinical trial evidence that this is when irritation is most likely to occur)
- Apply a gentle, non-comedogenic moisturizer
- Use a short contact method for the first 2–4 weeks (apply retinoid to full face for 30–60 min then wash-off). [5]

OPTIMIZING ACNE THERAPY:

From both the patient's and the clinician's viewpoint, the two major goals of acne therapy are:

- ✓ to achieve clearance or almost complete clearance of acne lesions and
- ✓ to minimize the potential for long-lasting acne-related sequelae such as scarring, PIH, and erythema.

Optimally, clearance should be sustained by a therapy that can prevent the majority of new lesion formation. A US study demonstrated that 43% of patients with active acne consulting a dermatologist have scars. As might be intuitive to clinicians, the likelihood of scarring increased with acne severity: 51% of moderate acne patients had scars, and 77% of severe acne patients had scars at the time of the acne consultation.

Acne often follows a chronic relapsing and remitting course, and it is important to have topical medications that decrease the formation of new lesions by targeting the micro-comedone, the precursor of acne lesions.

There are a variety of topical retinoid concentrations and formulations currently available, allowing clinicians to design individualized treatment regimens based on the patient's presentation, preferences, and ability to tolerate treatment.

Retinoids are also available in fixed-combination formulations with BPO [adapalene-BPO 0.1%/2.5% and 0.3%/2.5% (Epiduo® and Epiduo Forte®, Galderma Laboratories)] and clindamycin [tretinoin 0.025%/clindamycin phosphate 1.2% (Veltin, Aqua Pharmaceuticals; Ziana®, Valeant Pharmaceuticals)].

The use of retinoids plus BPO targets multiple pathways and can often eliminate the need for antibiotics, reducing the likelihood of antimicrobial resistance.

Dosage may be increased to improve efficacy, since a dose-dependent relationship has been shown for retinoids. Fixed-dose combination formulations can help to streamline therapy, which may be expected to positively impact adherence. (6)

The scientific rationale for use of topical retinoids in acne is clear. Clinical data from many thousands of patients show these agents are highly efficacious on both noninflammatory and inflammatory acne lesions. Expert groups and evidence-based guidelines agree that topical retinoids should be considered the foundation of acne therapy.

It is our hope that educational efforts can be made for all clinicians treating acne so that patients receive optimal therapy according to today's best practices. [7]

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