SUPPORTED BY AN UNRESTRICTED EDUCATIONAL GRANT FROM ORTHO DERMATOLOGICAL

The growing importance of topical retinoids in clinical dermatology: a retrospective and prospective analysis

Albert M. Kligman, MD, PhD *Philadelphia, Pennsylvania*

Topical tretinoin was the first of the retinoids to be launched into the channels of commerce for the treatment of acne vulgaris 30 years ago.[1] Since then there has been an explosion of interest in the therapeutic uses of retinoids, in both oral and topical formulations. This is reflected in the thousands of papers that have been published in medical journals in the last 15 years and by the synthesis of at least 2500 new retinoids by the pharmaceutical industry. In dermatology, retinoids are among the most exciting and important pharmacologic agents in light of their large presence on the therapeutic scene. The literature is rich in therapeutic reports detailing their successful usage. Nonetheless, the retinoid clinical era is still in an early stage of development. Basic studies of molecular mechanisms of action and biochemistry far outpace advances in therapeutics. If no more retinoids were added to the inventory, clinicians would still be busy for decades searching out new therapeutic applications in diverse areas of clinical medicine.

Initially, a retinoid was simply a compound whose structure and action resembled the parent compound, vitamin A (retinol). Vitamin A has been a dream molecule for the chemist who works with synthetics. Modifications may be readily made by substitutions at the carboxylic end group, the polyene chain, or the aromatic ring. We have witnessed the rapid and dramatic development of 3 generations of retinoids, the first being nonaromatic; the second, monoaromatic; and lastly, the polyaromatic (arotinoids). These were rationally developed based on a fundamental understanding of ligand-receptor linkages. This saga is the high point where basic science and clinical medicine merge. The latest retinoids bear little structural resemblance to retinol and qualify as a retinoid solely because they share 1 or more functions of the parent compound.

Retinoids have revolutionized the practice of dermatology, not to mention oncology. Scores of life-spoiling dermatologic disorders are now controllable and sometimes even curable—witness the often permanent resolution of acne conglobata by oral isotretinoin.

In contrast to the corticosteroid revolution at midcentury, dermatologists have played leading roles in the retinoid revolution 25 years later. The speed of developments has been breathtaking. Karrer et al[2] got the Nobel Prize for determining the structure of retinol in 1931. A mere 12 years later, retinol was successfully synthesized and soon became commercially available. The pharmaceutical industry deserves great credit for its visionary role in allocating powerful resources toward the use of retinoids in the prevention and treatment of diverse diseases. Compounds are being amassed at a rate far greater than they can be assayed for therapeutic uses. Clinician-investigators cannot keep pace with the evaluations of the agents they envision.

Special homage for pioneering efforts is due to Stuttgen,[3] a dermatologist in Berlin, and Bollag,[4] a researcher with Hoffmann-La Roche in Switzerland. They began to look at oral and topical retinoids in the 1960s as a means to treat a variety of dermatologic disorders. They presciently focused on hyperproliferative, hyperkeratotic disorders, such as psoriasis and ichthyosis. Early on they were able to demonstrate efficacy with oral retinol, but only at toxic levels. It was a natural step for a dermatologist to switch to a topical approach. Vitamin A acid, also known as retinoic acid or tretinoin, was a logical choice because it is a metabolic product of retinol, physiologically the

From the Department of Dermatology, University of Pennsylvania School of Medicine.

Reprint requests: Albert M. Kligman, MD, PhD, Department of Dermatology, University of Pennsylvania School of Medicine, 219 Clinical Research Bldg., 415 Curie Blvd., Philadelphia, PA 19104.

(J Am Acad Dermatol 1998;39:S2-7.)

0190-9622/98/$5.00 + 0 **16/0/91617**

active form. Tretinoin was subsequently shown to be beneficial in a variety of keratinizing disorders. Stuttgen and Bollag understood then, as we do now, that they were dealing with the pharmacologic effects of retinoic acid and not its original function as an essential vitamin. These discoveries were made empirically long before the pharmaceutical industry learned how to prepare stable formulations that would optimize release and penetration into the skin. The innovative Stuttgen failed to recognize the therapeutic value of tretinoin in acne vulgaris. The lesson from this misperception is that clinical investigation is a great deal more difficult and complex than many laboratory scientists suppose.

It was inevitable that retinoids other than tretinoin would become available for the treatment of keratinizing disorders. To gain physician acceptance and usage, new topical retinoids must demonstrate advantages over tretinoin, greater specificity for particular diseases, and less irritancy. Several of these agents have recently become available.

For example, adapalene, a new napthoic acid retinoid recently approved by the Food and Drug Administration for treatment of acne, has been shown to be less irritating, presumably enhancing compliance.[5] Another newcomer is tazarotene, an acetylenic retinoid that appears valuable in the treatment of psoriasis, producing long-lasting remissions.[6] It is worth noting that both of these agents are the result of basic research that focused on binding of the retinoid to specific nuclear receptors. Whether these new agents are more efficacious for their indications has yet to be demonstrated. In any case, this is a key demonstration that basic molecular research can lead to the development and approval of new agents.

Lately, there has been a rekindling of interest in the topical retinol, vitamin A itself, which Stuttgen and I originally discarded because of an apparent lack of effectiveness. However, recent investigations with retinol in the appropriate concentration and vehicle have shown that it is as effective as tretinoin for the same indications. The limiting factor of the early work was the instability of retinol—it was quickly rendered inactive by oxidation. Thus the formulated products had no shelf life. Because retinol is metabolically converted to retinoic acid, one would predict efficacy if oxidative degradation could be prevented. It is a tribute to the advances in pharmaceutical formulating that stable preparations of retinol have now become available. Because of regulatory peculiarities, retinol is an over-the-counter cosmeceutical product that does not require the Food and Drug Administration approval, although retinoic acid and other retinoids are prescription drugs.

A word of warning is in order regarding the uncritical use of retinoids in a great variety of unregulated skin care products. Retinyl palmitate is a case in point. It is topically ineffective but can be found in myriads of cosmeceutical products. Also, homeopathic doses of retinol and its esters are often listed on labels though there is no scientific proof of efficacy. Incorporating a miniscule amount of a retinoid into a cosmeceutical product has become a means by which manufacturers of these products have sought to gain medical legitimacy.

In Europe, isotretinoin, the *cis*-isomer of retinoic acid, is also available for topical use. History has something to teach us here. Stuttgen had found that oral retinoic acid was efficacious in keratinizing disorders, but like retinol, was far too toxic. I also had the same experience at a later time. Undaunted, Hoffmann-La Roche undertook the synthesis of derivatives of retinoic acid, looking for safer molecules. Astonishingly, seemingly minor structural changes to form the *cis*-isomer, 13-*cis*-retinoic acid, resulted in a new class of oral retinoids with extraordinary efficacy in severe acne. Peck and Yoder[7] demonstrated that isotretinoin could cure severe acne conglobata, which was a milestone in dermatologic drug discovery.

Acne conglobata is a terribly disfiguring disease that was formerly beyond the reach of the dermatologic armamentarium. To achieve a permanent remission in the worst form of acne surely justifies the journalistic description of a “breakthrough.” This development opened the floodgates to a host of new retinoids that transformed the dermatologic scene. Oncology has also been permanently changed by the successful use of retinoids in the treatment and prevention of cancer.

There is a quixotic footnote to the *cis*-retinoic story. The *cis*-isomer is available in Europe for topical use and matches tretinoin in efficacy. However, no American manufacturer will produce it, because of its association with congenital defects induced by oral use. All known oral

retinoids are teratogenic, including retinol. Extensive studies have shown no risk of teratogenicity with the topical formulation.

FUTURE PROSPECTS

Retinoids are remarkable drugs in that their pharmacologic effects are so extraordinarily multifarious. They act in different ways on a host of unrelated disorders. An acceptable explanation for the diverse biologic actions of the retinoids is not at hand. They must be acting at a critical, early stage in the pathogenesis of disease. However, some insights are available for discussion. The concept of nuclear retinoid receptors has powered an immense amount of research into mechanisms of action.

This is not the place to summarize the advances that basic scientists have made in the molecular mechanisms of retinoids. Three recent reviews will bring the interested reader to a high level of appreciation of the pharmacologic properties of and biochemistry of retinoids. These are "Retinoids and the Skin" by Futoryan and Gilchrest,[8] "Current Use and Future Potential Role of Retinoids in Dermatology" by Orfanos et al,[9] and "Retinoids and Keratinocyte Differentation In Vitro" by Stadler et al.[10]

We turn now to clinical matters that depict the present and future therapeutic scene. The expanding scope of topical retinoids in dermatologic diseases can be appreciated by looking at the inventory of therapeutic usages for retinoic acid compiled by Thomas and Doyle in 1981.[11] They came up with a little more than a dozen applications, emphasizing acne, solar keratoses, ichthyosis, psoriasis, lichen planus, melasma, and a few less-important conditions.

My current inventory encompasses about 125 distinctive dermatologic disorders for which there is credible evidence of efficacy. I found over 150 articles that proclaimed benefits from topical tretinoin (not all supported by scientific proof). I predict that clinical investigators will make a convincing case for the use of retinoids in many disorders where the evidence is promising but still preliminary.

The pace of proving the promise is slow because of the preoccupation of medical journal editors for double-blind, placebo-controlled studies as the visa for publication. No one can question the desirability of such studies, but there is also no question that such strict requirements inhibit innovation. I cite 2 great advances in dermatologic therapeutics that came out of empirical "unscientific" efforts by creative dermatologists in their office practice, namely, 5-fluorouracil for actinic keratoses and methotrexate for psoriasis. An enduring virtue of national medical conferences and symposia is that one can listen in the corridors to the unpublished experiences of enterprising, imaginative clinicians. Academicians may take years to validate the interesting findings of practitioners.

It is impossible to cite the scores of recently published papers that indicate the enormous range of therapeutic possibilities of retinoids in common and uncommon dermatologic disorders. Instead, I will reduce the universe of possibilities to 2 graphic figures, which I shall call the solar spectrum of retinoids.

Fig. 1 illustrates the biologic diversity of pharmacologic activities of the retinoids. This is only a partial listing, which makes the growth of knowledge even more astonishing. It is tempting to explain all this diversity in mechanistic reductionist terms that have the authenticity of scientific doctrine. For example, many works show that retinoids interact with cytosolic proteins and 2 classes of nuclear receptors, RAR and RXR, members of the steroid-thyroid hormone family. Retinoids act as ligand-dependent transcriptional factors that induce expression of genes bearing specific DNA sequences.

These formidable expositions may be largely true, but they do not satisfactorily explain the phenomena of biologic diversity. It is all too easy to generalize, but it is also noteworthy that not all retinoids act through binding to nuclear receptors. Acitretin, a new antipsoriatic drug, may be such an example. Other mechanisms that may supplement the receptor concept are still to be discovered.

How can one class of drugs have such a wide range of seemingly unrelated activities? Retinoids are always described as being essential for the growth, differentiation, and maintenance of epithelial tissues. Such descriptive statements provide no enlightenment about how retinoids exert various immunomodulatory effects such as the stimulation of humoral and cell-mediated immunity. It seems as if not a week goes by without a discovery that retinoids have still another function in the cascade of events that characterize immunologic responsiveness.

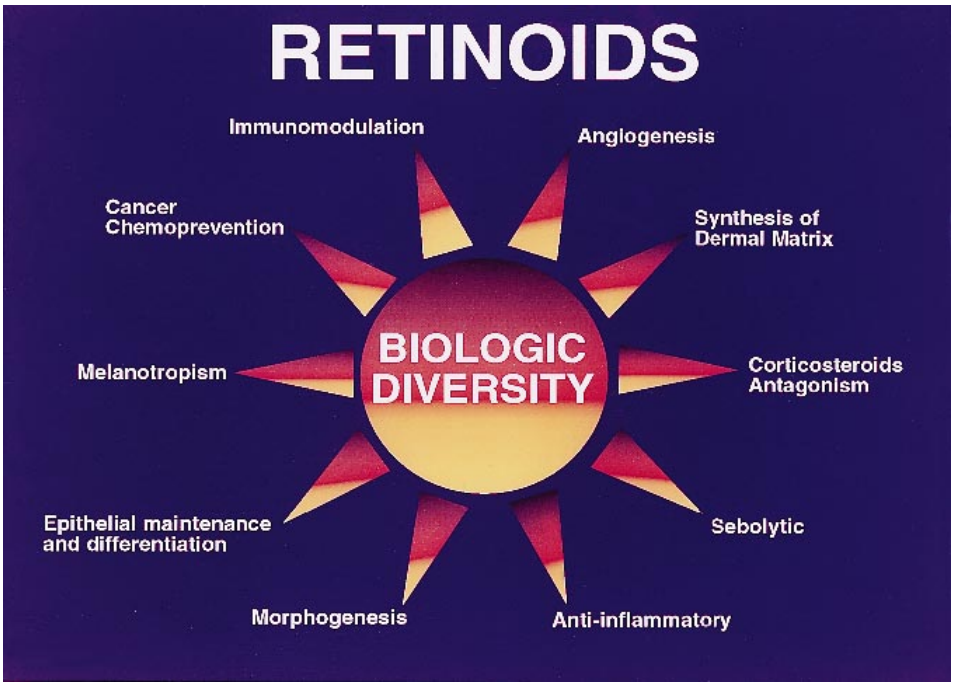

Fig. 1. The spectrum of biologic diversity of the retinoid universe.

Perhaps the antineoplastic use of retinoids outshines all others in clinical importance. It was shown early on that topical tretinoin had a beneficial effect on precancerous or cancerous neoplasms.[4] Various systemic treatment regimens have achieved high success in devastating cancers, often in combination with other anticancer agents such as 5-fluorouracil and the interferons. Of even greater importance is the recent awareness of the usefulness of the retinoids in the prevention of cancer. This is a new field of paramount importance, subsumed under the rubric of chemoprevention. Retinoids have much to offer in the field of chemoprevention, which includes many competitive approaches such as antioxidants, free radical scavengers, macronutrients, and others.

The category of anti-inflammatory activity of the retinoids has barely begun to receive acceptance. The clinical evidence of an anti-inflammatory action is unmistakable in such diseases as acne and psoriasis, but the mechanism of action remains unknown. Corticosteroids are the prototype of anti-inflammatory drugs, but retinoids clearly act in a totally different way. At present, how they counteract inflammation is purely speculative, involving a variety of indirect mechanisms. One that has recently come to the fore is apoptosis, or programmed cell death. This is now seen to be operative in a wide range of conditions, such as cancer, wound healing, and aging.

It follows from the multiplicity of actions that clinical applications will be even greater in number, because the same agent may beneficially affect different diseases. Fig. 2 lists a few of the skin disorders that unequivocally respond to topical retinoids. At first glance some, like rosacea, are surprising, even paradoxic, because patients with rosacea are thought to have unusually “sensitive” skin. However, when one realizes that rosacea is, among other things, photodermatosis, always showing severe photoaging changes histologically, its good response to topical retinoids is easily understood.

It is much easier to explain the beneficial effect in acne, because tretinoin is strongly comedolytic, sebolytic, and also anti-inflammatory. These are concomitant processes involved in the pathogenesis of acne.

For those of us who have the old-fashioned idea that empiricism or trial-and-error approaches still have a place in opening up novel therapeutic possibilities, the case of hypertrophic scars is instructive. Tretinoin is known to stimulate the synthesis of collagen, which is excessively deposited in hyper-

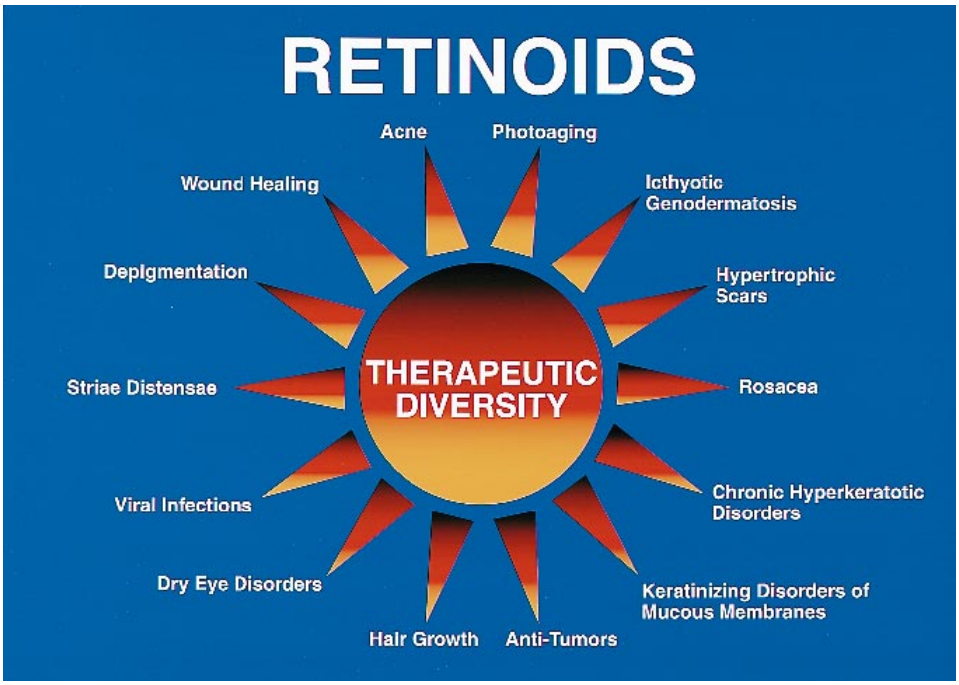

Fig. 2. The clinical spectrum of retinoids.

trophic scarring. Nonetheless, it seems to work in many cases—an apparent contradiction. However, scars involve many cells other than hypermetabolizing fibroblasts, namely, mast cells, activated T cells, and macrophages. Acne scars are active and not burned out, as commonly thought. Tretinoin acts on many cell types. The take-home message here is that the amelioration of a disease depends on the pathogenic peculiarities of that disease. In any case, theory must give way to empiric demonstrations, until research reconciles the paradox.

There is a plethora of retinoids, most of which have not been put to the clinical test. We do need to develop models, preferably in vitro ones, that can screen retinoids for various activities when coupled with computerized programs, some of which are already online.

Many clinicians have little awareness of the many different disorders in which the prototype tretinoin may be beneficial. Used in combination with other topical or oral drugs, the capabilities of tretinoin to moderate chronic cutaneous disorders are expansive. This is a wake-up call for clinician-investigators to try these combinations on puzzling and refractory cases. For example, low oral doses of *cis*-retinoic acid in combination with topical tretinoin have yielded striking benefits in dealing with myriads of tumors that develop in patients who are immunosuppressed and have experienced renal homograft,[12] disseminate actinic keratoses,[13] and severe facial photoaging.[14]

An untapped gold mine is the combination of topical corticosteroids and tretinoin in chronic dermatoses, notably stubborn plaque-type psoriasis. I find that alternate-day regimens offer effective therapy; for example, a mid- to high-potency steroid twice a day on Monday, followed by 0.1% tretinoin cream twice a day on Tuesday, then back to the steroid on Wednesday, and so on. This minimizes potential interactions associated with the use of same-day combination therapy. I also favor steroid-sparing regimens for atopic dermatitis in which unmedicated old-fashioned moisturizers are given twice on 1 day and midstrength corticosteroids on the alternate days.

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