The Egyptian Journal of Hospital Medicine (January 2022) Vol. 86, Page 641-644

An Overview of Role of Retinoids in Management of Warts: Review Article

Ahmad Nofal, Samar Mohammad Mohammad Najah*, Ahmed Said Abdel Shafy
Department of Dermatology, Venereology and Andrology, Zagazig University Hospital, Egypt
***Corresponding author:** Samar Mohammad Mohammad Najah, **E-Mail:** mohammedsamar512@gmail.com

ABSTRACT
Background: Human papillomavirus (HPV)-inducing HPV-types can cause a wide range of cutaneous wart morphology and histological patterns that are distinct from one another. Certain forms of warts are more commonly related with various HPVs that cause cutaneous warts. It is essential that treatments for different forms of warts are both safe and painless. As warts can resolve up to two-thirds of the time without treatment, and treatments should not increase morbidity, this is particularly significant. In contrast, a large number of warts do not self-resolve fast and are associated with diminished quality of life, embarrassment, and pain in the skin. In terms of structure and function, retinoids resemble vitamin A in many ways. Both the differentiation and proliferation of keratinocytes and the immune system are hampered by their immunomodulatory effects.
Objective: Assessment of role of retinoids in management of warts.
Conclusion: Oral retinoids such as isotretinoin and acitretin are safe and reported to be effective therapy for different types of warts.
Keywords : Human papillomavirus, Retinoids, Warts

INTRODUCTION

Human papillomavirus (HPV) infection of the skin is extremely common. Warts are noncancerous skin growths caused by HPV infection (verrucae). The rapid proliferation of cells on the outer layer of the skin is what causes warts. Even while warts have been documented since ancient Greece, it wasn't until 1907 that the virus responsible for their development was identified [(1)].

These skin warts normally form and then disappear over the course of a few weeks or months. There are many cases of warts that recur on the skin. Small numbers of skin-derived stem cells may harbour long-term "latent" infections from any one of the HPVs. Although these latent infections may never be completely eliminated, immune management is expected to prevent symptoms like warts from developing. It is possible for a person to grow resistant to one HPV type while still being susceptible to other HPV kinds [(2)].

A cure for warts has eluded scientists for decades, despite extensive research. There is no one treatment that works for all warts, thus new treatment options are constantly being developed. Approximately 9.1 percent to 21.7 percent of dermatological referrals are for the treatment of cutaneous warts in primary school students [(3)].

The treatments for different forms of warts must be safe and, if possible, not painful. As warts can resolve up to two-thirds of the time without treatment, and treatments should not increase morbidity, this is particularly significant. In contrast, many warts don't promptly self-resolve, resulting in a lower quality of life, shame, as well as physical suffering for the patient [(4)].

Received: 7 /9 /2021
Accepted: 4 /11 /2021

Figure (1): Treatments of warts [5].

Retinoids in Treatment of Warts:

Chemically, the retinoids belong to the vitamin A vitamer or similar class of chemicals. In medicine, retinoids are used to govern the proliferation of epithelial cells. In addition to their roles in vision and cell proliferation and differentiation, retinoids also play essential roles in the development of bone tissue, the immune system, and the activation of tumor-suppressor genes [6].

They're also being tested for their capacity to treat skin cancer. Tretinoin is used to treat acute promyelocytic leukemia, while alitretinoin (9-cis-retinoic acid) is used to treat skin lesions from Kaposi's sarcoma [7].

Chemical structure of Retinoids:

Vitamin A is the starting point for the synthesis of retinoids. Cell division and development of epidermal stratified structures are influenced by these factors. Natural retinoids, such as vitamin A (retinol), its provitamin (carotene), and its aldehyde (retinal) and acid (all-trans-retinoic acid ATRA) forms, play an important role in many vital biological processes, including vision, reproduction and vertebrate embryonic morphogenesis and organogenesis, cell growth arrest, cell differentiation and apoptosis [8].

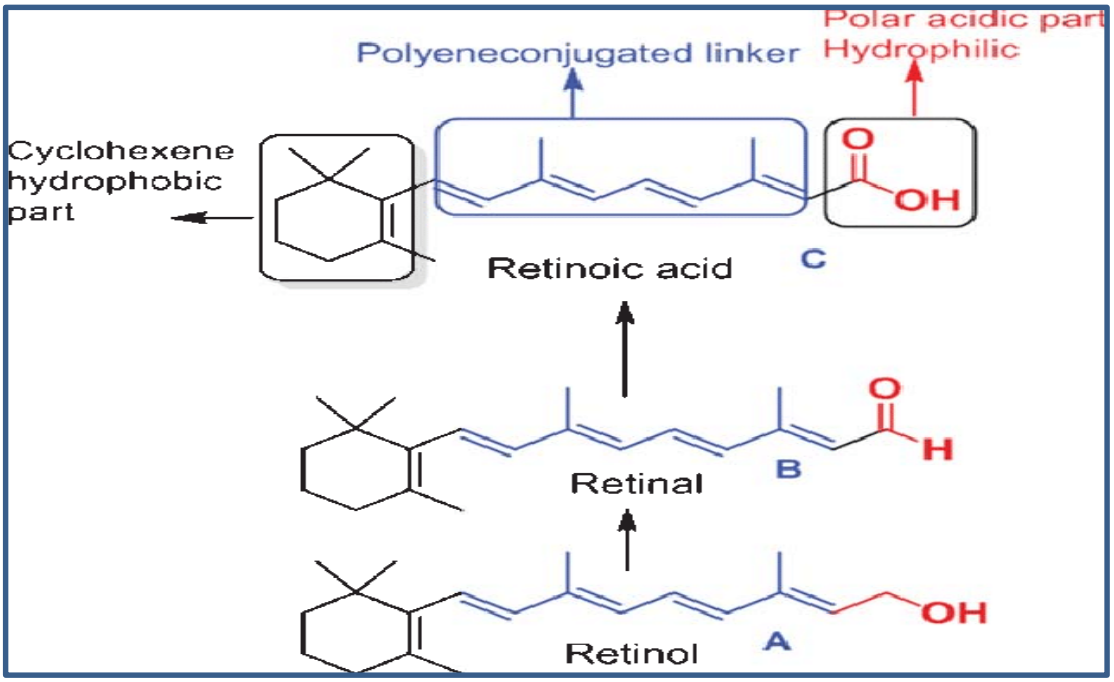

Figure (2): The basic structure of retinoids [7].

It has a polyene side chain and an end group with three cyclic end groups, making it hydrophobic. Conjugated system of C=C double bonds in the polyene side chain is responsible for retinoids' hue (typically yellow, orange, or red). There are numerous examples of this, as many retinoids are chromosomes. The different retinoids are created by varying the side chains and end groups [(9)].

They are able to interact with a wide range of receptors because of the flexibility provided by their double bonds, which alternate between single and double bonds. Due to their inflexibility, third- and second-generation retinoids don't interact with as many receptors as first- and second-generation ones. It is trifarotene, a fourth-generation retinoid that binds to the RAR-y receptor [(7)].

Types of Retinoids:

Retinoids can be divided into four generations:

A retinol, retinal, retinoic (retinoic acid), isotretinoin, and alitretinoin are the first generation of retinols, etretinate and acitretin, a byproduct of etretinate, are included in the second generation, adapalene, bexarotene, and tazarotene are examples of the third generation, Trifarotene has been included to the fourth generation. Retinoids generated from pyranones are sometimes referred to as the "fourth generation" by some researchers. Seletinoid G is one such chemical [(10)].

Pharmacokinetics and pharmacodynamics:

Acitretin:

Pharmacodynamics:

The lack of an appropriate experimental paradigm has limited the study of acitretin's pharmacological features. Acitretin reduces epidermal cell growth and differentiation in cultures of hyperproliferative diseases like psoriasis or neoplasia and controls cell proliferation in vitro using normal human skin fibroblasts [(9)].

Several well-established or transplantable cancer cell lines are inhibited or regressed in growth and development by acitretin, which also suppresses chemically-induced hyperplasia. In hyperproliferative illnesses, the mechanism of acitretin's activity has yet to be fully understood; however, it appears to have numerous cellular effects. A number of other proteins and nucleic acids have been proposed as potential targets for this drug, including CRABP, EGF, and nuclear retinoic acid receptors (RARs) **[(7)].**

Acitretin increases CRABP levels in normal epidermis by binding competitively to the protein seen in high amounts in psoriatic plaques. 13-cis-acitretin, on the other hand, does not bind to CRABP, therefore it is possible that acitretin works by activating RARs after being converted into a molecule that does [(10)].

Acitretin has been shown to affect the EGF receptor's ability to regulate cell proliferation in both normal fibroblasts and cancerous cell lines. The clinical response is likely mediated by cAMP-dependent protein kinases and ornithine decarboxylase **[(9)].**

The anti-inflammatory and immunomodulatory properties of acitretin have also been shown. Anti-polymorphonuclear leukocyte accumulation, suppression of lymphocyte blastogenesis and activation of T cell-mediated cytotoxicity are suggested to be the mechanisms **[(10)].**

In pharmacokinetics:

Peak plasma acitretin concentrations range from 98 to 526 µg/L and are achieved roughly 1.9 hours after a single 40 mg dose in patients with psoriasis. About 60% of acitretin's total bioavailability is found throughout the body. CRABP has a strong binding affinity for this protein because of its broad albumin binding **[(11)].**

Acitretin has a shorter terminal elimination half-life than etretinate because it is less tightly coupled to lipoproteins (less than 5%), making it less likely to be stored in fatty "deep" storage sites. Acitretin and 13-cis-acitretin are no longer detectable in plasma three to four weeks after the end of long-term therapy, according to multiple dosage trials [(11)].

Acitretin undergoes significant isomeric interconversion after oral treatment; 13-cis metabolite maximal plasma concentrations are lower and occur significantly later than those of acitretin. This metabolite has a terminal elimination half-life that is roughly 15 times longer than acitretin's parent drug and plasma trough concentrations that are about 5 times greater [(10)].

Glucuronides in bile and products with shorter side chains in urine are the most common excretion forms of acitretin. Acitretin and three additional metabolites have been found in blood samples. Etretinate has been found in plasma samples from patients receiving acitretin through liquid chromatography and mass spectrometry **[(9)].**

It's possible that the findings thus far could have teratogenic consequences for female patients. Until these fresh results are clarified, it is advisable to increase the post-therapy contraceptive duration to 2 years instead of the 2 months originally indicated [(7)].

Isotretinoin:

High-fat meals are optimal for absorbing oral isotretinoin because of its lipophilicity. After a high-fat meal, isotretinoin's effectiveness doubles, compared to when it's not taken at all. It is not recommended that isotretinoin be used with vitamin A supplements because of the risk of toxicity from cumulative overdose caused by their molecular connection **[(10)].**

99.9 percent of the isotretinoin in the bloodstream is linked to plasma proteins, most notably to albumin. After oral administration of isotretinoin, the

metabolites 4-oxo-isotretinoin, retinoid acid (tretinoin), and 4-oxo-retinoic acid can be detected in human plasma. It is also oxidised to 4-oxo-isotretinoin, which is its geometric isomer of 4-oxo-tretinoin, irreversibly by isotretinoin. Isotretinoin and its conjugates are then eliminated in nearly equal levels in the urine and feces of the individual [(7)].

Mechanism of action of Retinoids:

After retinol is converted to retinaldehyde in the target cell, a two-step process produces RA and 9-cis-retinoic acid, which are important active natural metabolites. An important step forward in understanding the mechanism of action of retinoids was made possible by the discovery of the nuclear retinoic acid (RA) receptors that belong to the nuclear receptor superfamily [(10)].

A natural ligand for RA receptors (RAR) and 9-cis-retinoic acid-receptors (RXR) can be found in the retinoid nuclear receptor (RNR) families. Bexarotene, the first rexinoid (a RXR ligand), and alitretinoin, the first panagonist (an RAR+RXR) are all examples of synthetic retinoids that have been shown to interact with the Retin-A Receptor (RAR) [(11)]. As a rule, there are three isotypes for each family and many isoforms for every isotype. There are six regions in each NRR (A-F) [(7)].

Target genes' promoters include a specific sequence of DNA, which dimers bind to. When a ligand, whether natural or synthetic, binds to RNR, coactivators are recruited and transcription factors are activated. Activated cytochrome P450 enzymes in the target cell degrade retinoids into their inactive polar metabolites [(9)].

Side effects of Retinoids:

Mucocutaneous side effects, liver toxicity, and aberrant lipid profiles in the blood may be linked to an elevated risk of coronary heart disease when retinoids are administered systemically. Women who are pregnant or want to become pregnant should avoid any retinoids because of their teratogenic effects. Skeletal abnormalities may be caused by long-term retinoid therapy-induced chronic toxicities, which frequently match the symptoms of diffuse idiopathic hyperostosis syndrome [(11)].

Premature epiphyseal closure may also be a side effect of long-term retinoid treatment in youngsters. Unlike other retinoids' adverse effects, which are dose-dependent and reversible when the medication is stopped, bone abnormalities are unlikely to go away when retinoids are stopped [(9)].

Treatment with retinoids necessitates cautious patient selection, rigorous benefit-risk analysis for each individual, and ongoing clinical response and laboratory testing monitoring due to the wide range of toxicities. Side effects can be avoided or minimised with the application of particular management strategies. The development of novel retinoids with improved therapeutic efficacy and less adverse responses is currently the subject of extensive research [(7)].

CONCLUSION

Oral retinoids such as isotretinoin and acitretin are safe and reported to be effective therapy for different types of warts.

Financial support and sponsorship: Nil.
Conflict of interest: Nil.

REFERENCES

1. **Ghadgepatil S, Gupta S, Sharma Y (2016):** Clinicoepidemiological study of different types of warts. Dermatology Research and Practice, 16: 7989817.
2. **Loo S, Tang W (2014):** Warts (non-genital). https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4054795/
3. **Nanda S, Fayne R, Zaiac M (2020):** Warts. In Therapies for Nail Disorders. CRC Press. pp. 156-167. https://www.researchgate.net/publication/339920046_Warts
4. **Friedman P (2021):** Management of difficult-to-treat warts: Traditional and new approaches. American Journal of Clinical Dermatology, 22(3): 379-394.
5. **Majid M (2020):** Cutaneous warts treatment modalities. Indian J Dermatol., 58:360–5.
6. **Kiser P, Golczak M, Palczewski K (2014):** Chemistry of the retinoid (visual) cycle. Chemical Reviews, 114(1): 194-232.
7. **Shalita A (2001):** The integral role of topical and oral retinoids in the early treatment of acne. Journal of the European Academy of Dermatology and Venereology, 15: 43–9.
8. **Nofal A, Mohammed N, Khater E (2021):** Role of systemic retinoids in the treatment of warts. Turkish Journal of Physiotherapy and Rehabilitation, 32: 3-6.
9. **Pendino F, Flexor M, Delhommeau F (2001):** Retinoids down-regulate telomerase and telomere length in a pathway distinct from leukemia cell differentiation. Proceedings of the National Academy of Sciences of the United States of America, 98(12): 6662–7.
10. **Yurdakok B, Filazi A, Ince S (2017):** Retinoids. In Reproductive and Developmental Toxicology. Academic Press. Pp. 481-492. https://www.researchgate.net/publication/315786404_Retinoids
11. **Zasada M, Budzisz E (2019):** Retinoids: Active molecules influencing skin structure formation in cosmetic and dermatological treatments. Advances in Dermatology and Allergology/Postępy Dermatologii i Alergologii, 36(4): 392-96.