ROLE OF SYSTEMIC RETINOIDS IN THE TREATMENT OF WARTS

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ABSTRACT

Background: Warts are common benign tumors caused by human papillomavirus (HPV) infection, which is acquired from direct contact with an infected individual or from the environment. The current modalities of wart treatments such as chemical therapy, electrodessication, cryotherapy and laser therapy depend on the ablation of warts and are commonly associated with significant pain, tissue destruction, scarring and high recurrence rate and these modalities are not practical for patients presenting with a large number of warts. Systemic retinoids, including acitretin and isotretinoin have been recently proposed as promising, effective, well tolerated and non-invasive alternative modalities for the treatment of multiple and recalcitrant warts. The aim of this article is to review the efficacy of systemic retinoids in the treatment of warts. Conclusion: systemic retinoids are effective in the treatment of warts and they are well tolerated, non-invasive alternative modalities with few adverse effects.

Key words: warts, HPV, systemic retinoids, acitretin, isotretinoin

I. INTRODUCTION

Warts are benign epidermal tumors caused by human papillomaviruses (HPVs). They are associated with significant physical and psychological discomfort. HPV infect keratinocytes and induce hyperplasia and hyperkeratosis. This increased growth forms a wart. HPV cause both genital and cutaneous warts [1]. Warts are classified according to their appearance or site into different types such as common warts, plane warts, plantar warts, and genital warts. Warts often cause significant discomfort and embarrassment [2].

Current modalities of wart treatments

Multiple modalities are available for the treatment of warts. Each therapeutic method has variable rate of success and adverse effects. No treatment has consistent efficacy for all patients. Treatment should be started if the wart is symptomatic or causes psychological distress, if there are many lesions or if lesions are large, if the patient requests therapy or is concerned about transmission to others or self, or if the patient is immunocompromised. The treatment modality should have benign side effect profile and low cost [3]. The current modalities of wart treatments such as chemical therapy, electrodessication, cryotherapy and laser therapy depend on the ablation of warts.

They are commonly associated with significant pain, tissue destruction, scarring, high recurrence rate and are not practical for patients presenting with a large number of warts [4,5]. On the other hand, immunotherapeutic agents include contact sensitizers such as diphencyprone, immunomodulatory agents such as imiquimod, intralesional interferons, and oral drugs such as levamisole, cimetidine, and zinc sulphate. Other modalities include anti-proliferative agents as 5-fluouracil and bleomycin, antiviral drugs such as intravenous cidofovir, systemic retinoids, and hypnotherapy [6,7].

Systemic retinoids, including isotretinoin and acitretin have potent immunomodulatory, anti-inflammatory and apoptotic effects. They have also been proposed to modulate keratinocytes growth and differentiation and proliferation, and downregulate HPV [8, 9]. It has also been postulated that systemic retinoids may play a role in the treatment of HPV due to its anti-angiogenic properties via a reduction of vascular endothelial growth factor production by keratinocytes [10].

Acitretin and isotretinoin have been proposed by some authors as promising, effective, well tolerated and non-invasive alternative modalities for the treatment multiple and recalcitrant warts [11,12,13]. They have the advantage
of acceptable cost, easy intake, extended remission time, and infrequent relapses, either alone or in combination with other conventional therapies such as tretinoin [14], and intralesional immunotherapy such as Candida antigen [15].

Table (1): Available treatments for warts (15)

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<td>B) Antimitotic Drugs</td>
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<td>C) Immunotherapy</td>
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<td>Topical immunotherapeutic agents e.g. imiquimod</td>
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<td>Intralesional immunotherapy e.g. Candida antigen</td>
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II. STRUCTURE OF SYSTEMIC RETINOIDS

Retinoids are chemically derived from vitamin A. They influence cellular division and differentiation of stratified structures of epidermis. Vitamin A (retinol), its provitamin (β-carotene) and its aldehyde (retinal) and acid (all-trans-retinoic acid ATRA) forms are all-natural retinoids and are involved in a wide variety of essential biological processes, such as vision, reproduction, vertebrate embryonic morphogenesis and organogenesis, cell growth arrest, cell differentiation, apoptosis and immune regulation [16].

![Chemistry of Retinoids](image)

**Figure (1):** Structure of systemic retinoids [16].

**Pharmacokinetics and pharmacodynamics**

Retinoid metabolism is achieved through oxidation, chain shortening, and hepatic processing into water-soluble, biologically inert products. Whereas isotretinoin is initially oxidized to 4-oxo-isotretinoin, acitretin first undergoes isomerization followed by oxidation. This results in the distinct metabolic byproducts of acitretin, 13-trans and 13-cis acitretin, which are eventually eliminated in the bile and through the kidneys as soluble metabolites. Thus, adequate renal function is necessary for the complete excretion of acitretin metabolites, but not for isotretinoin. Additionally, acitretin is not removed by hemodialysis [17].
III. MECHANISM OF ACTION OF SYSTEMIC RETINOIDS

Retinoids exert their physiologic effects by binding specific nuclear receptors that belong to a superfamily of glucocorticosteroid, thyroid hormone, vitamin D and peroxisome proliferator-activated receptors [18]. Oral retinoids, apart from being a potent immunomodulator, they seem to have an antiproliferative effect in the HPV-induced epithelial hyperplasia, probably resulting either from changes in keratinocyte differentiation, antiviral activity (downregulate viral replication) or increase of killer T cells [19]. Oral retinoids may play a role in the treatment of HPV due to its antiangiogenic properties via a reduction of vascular endothelial growth factor (VEGF) production by keratinocytes. Therefore, systemic retinoids may have a great potential for treating angiogenesis dependent warts [10].

Retinoids also play a critical role in development, tissue homeostasis, differentiation, proliferation, and apoptosis. Systemic retinoid concentration was previously reported to be inversely associated with the levels of HPV DNA in patients with warts suggesting a downregulation of viral replication by retinoids [20].

Systemic retinoid modulates transcriptional regulation of keratinocyte genes to normalize epithelial differentiation and inhibit keratinocyte hyperplasia (a hallmark of HPV infection). As HPV replication is dependent on accelerated keratinocyte differentiation, retinoid induced changes in keratinization act to down regulate viral replication [19].
Clinical trials for wart treatment with systemic retinoids

Dave and Abdelmaksoud[21], have shown 100% complete clearance of warts in 14 patients (12 with common warts, 1 with plane warts and one with venereal warts) after addition of a low dose of isotretinoin (0.1-0.2 mg/kg/day) to conventional therapeutic modalities. On the other hand, Gupta et al. [14], have reported a complete clearance of common warts in 3 out of 15 patients (20%) who have received a combination of tretinoin and oral isotretinoin at a dose of 20 mg/day. Nofal et al., [13], have treated 36 patients with multiple plane warts and showed complete response in 16 (44.4%) of them

El Gharib et al. [22] have shown an 80% clearance of common warts in response to acitretin (1 mg/kg/day). Acitretin has shown promising efficacy for the treatment of recalcitrant warts in individual case reports in both immunocompetent patients. A high clearance rate has been reported by other authors who have used acitretin for treatment of warts Kim et al. (48%) [23] , Zhang et al. (42.9%)[24] , Nofal et al. (40%)[9] , and Nofal et al. (38.9%)[15]. Similarly, Gelmetti et al. [25] in 1987 have also reported complete clearance of longstanding multiple and resistant viral warts in 16 out of 20 (80%) immunocompetent children by the closely related compound "etretinate."

Adverse effects of retinoids

Systemic retinoids are known to exert a number of adverse events. Most of the adverse events are dose dependent and reverse back to normal after decreasing the dose or after discontinuation of therapy. However, it is usual to have the minor side-effects on the long-term treatment with retinoids. The most common adverse effects of retinoids are the mucocutaneous adverse effects. Dry lips are the most common one and can be treated with the use of emollients. Others include dry mouth, cheilitis, stomatitis and gingivitis and taste disturbances. Acitretin causes dryness with inflammation of mucous membrane and transitional epithelia which occasionally leads to epistaxis, rhinitis, photophobia, conjunctivitis, and xerophthalmia. Alopecia and nail-fragility have also been observed. Mucocutaneous side effects can be treated symptomatically, and if severe effects occur, the dose reduction can be tried before the discontinuation of the drug [26].

Hyperlipidemia is the most common systemic side effect of retinoids. The elevation of triglyceride occurs in 50% of the patients taking isotretinoin or acitretin. Hypertriglycerideridemia is more likely to occur in patients with predisposing factors such as diabetes, obesity, alcohol intake, or a family history of these conditions. These effects are reversible and can be managed by dietary modifications, oral hypolipidemic drugs or decreasing retinoid dose [27,28]. Use of retinoids may cause transient and reversible elevation in serum liver enzymes up to 15% of patients. However, severe hepatotoxic reactions (severe cholestatic hepatitis/cirrhosis) and overt chemical hepatitis are rare (0.26%). Frequent monitoring of liver function is recommended in alcoholics, diabetics, obese individuals, and patients with concurrent use of other hepatotoxic agents [28]. Retinoids also cause blurring of vision, headache and reduced night vision. Patient with a severe headache, vomiting, and visual disturbances should stop retinoids immediately and consult the doctor [26].

Osteoporosis and premature epiphyseal closure in children have been reported with chronic vitamin A toxicity [27]. Alopecia and telogen effluvium due to the use of systemic retinoids have been reported. Hair loss is more seen with acitretin than with etretinate, while it is less reported with isotretinoin and bexarotene. Hair loss is a dose dependent and it is reversible in 2 months after reducing the dose or discontinuing therapy [29].

Isotretinoin, acitretin, etretinate and bexarotene are all classified by FDA in category X and are absolutely contraindicated during pregnancy. Adverse pregnancy outcomes such as spontaneous abortion, premature fetal death have been reported. Pregnancy should be excluded with at least one negative pregnancy test before retinoid therapy [27,30]. Retinoids have been associated with the following embryopathies: microcephaly, hydrocephalus, microophthalmos, cardiac septal defects and complex heart malformations, abnormalities of the ear and acral skeleton, craniofacial and thymus gland anomalies [31].

Adequate contraception (ideally two methods) is mandatory from at least one month before retinoids therapy up to 1 month after cessation of bexarotene and isotretinoin and 3 years after the cessation of acitretin [32].
Systemic retinoids have been recently investigated for the treatment of multiple and recalcitrant warts and have been proposed by some authors as promising, effective, well tolerated and non-invasive alternative modalities for the treatment of multiple and recalcitrant warts.

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