Ionic Contraviral Topical Therapy in Multiple Resistant to Treatment Verruca Vulgaris

Thesis

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Dedication

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List of Abbreviations

Abb.	Full term
5-FU	5-flurouracil
AK	Actinic keratosis
ALA	Aminolaevulinic acid
APCs	Antigen presenting cells
BCG	Bacillus Calmette-Guérin
BIP	Bleomycin –induced pneumonitis
BP	Bowenoid papulosis
CIN	Cervical intraepithelial neoplasia
CIS	Carcinoma in situ
CO2	Carbon Dioxide
DC	Dendritic Cell
DCP	Diphenocyprone
DNA	Deoxyribonucleic acid
DNCB	Dinitrochlorobenzene
DPCP	Diphenylcyclopropenone
E	Early region
EBV	Epstein Barr virus
ECT	Electrochemotherapy
Er:YAG	Erbium: Yttrium/Aluminum/Garnet
EV	Epidermodysplasia verruciformis
FEH	Focal epithelial hyperplasia
HIV	Human immunodeficiency virus
HPV	Human papilloma virus
IFNS	Interferons
IL	Interleukin
KS	Kaposi sarcoma

List of Abbreviations Cont...

Abb.	Full term
LCR	Long control region
LCs	Langerhans Cells
LN2	Liquid nitrogen
MC	Molluscum contagiosum
MRNA	Messenger Ribonucleic acid
Nd:YAG	Neodymium: Yttrium/ Aluminum/ Garnet
NEH	Neutrophilic Eccrine Hidradenitis
OHL	Oral hairy leukoplakia
PDL	Pulsed Dye Laser
PDT	Photodynamic Therapy
PIN	penile intraepithelial neoplasia
PPD	purified protein derivative
PPECs	Palmoplantar epidermal cysts
RRP	Recurrent respiratory papillomatosis
SA	Salicylic Acid
SADBE	Squaric acid dibutyl ester
SCC	Squamous cell carcinoma
TB	Tuberculosis
TCA	Trichloroacetic acid
TNF-α	Tumor necrosis factor alpha
VAIN	Vaginal intraepithelial neoplasia
VIN	Vulvar intraepithelial neoplasia
WHIM	Warts, Hypogammaglobulinemia, Infections and Myelokathxis

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INTRODUCTION

Common warts are small, rough skin growths that occur most often on fingers or hands. Common warts often feature a pattern of tiny black dots, which are small clotted blood vessels ***(Goldstein et al., 2015).***

Children and young adults are more likely to develop common warts. Common warts usually disappear on their own, but many people choose to remove them because they find them bothersome or embarrassing ***(Ferri et al., 2015).***

The virus usually spreads through breaks in the skin such as a hangnail or a scrape. Biting nails also can cause warts to spread on fingertips and around nails. Each person's immune system responds to the HPV virus differently, so not everyone who comes in contact with HPV develops warts ***(Kwok et al., 2015).***

Viral warts are caused by the human papilloma virus (HPV), with the most prevalent HPV genotypes being HPV 1, HPV 2, HPV 27 and HPV 57 ***(Bruggink et al., 2012).***

Efficacy rates of current treatment options, for example cryotherapy, salicylic acid and monochloroacetic acid, are low (cryotherapy 39%; salicylic acid 24%; monochloroacetic acid 46%), and cure rates are dependent on HPV type ***(Berger et al., 2010)***.

As efficacy rates of current treatment options are not optimal, side-effects are common, and recurrences often occur. There is an unmet need to develop new therapeutics for common warts. It has been shown that DNA viruses such as HPV rely on K^+ influx for replication, this could provide a therapeutic option ***(Hartley et al., 2013)***.

Both digoxin and furosemide inhibit the K^+ influx by interacting with cell membrane ion co-transporters (Na^+/K^+-ATPase and Na^+-K^+-$2Cl^-$ co-transporter-1, respectively). It can therefore be hypothesized that these two compounds in a topical formulation may be valuable in the treatment of HPV-induced warts. This new approach, called Ionic Contra-Viral Therapy (ICVT), has already shown inhibitory effects on DNA replication *in vitro*, with the strongest effect when digoxin and furosemide were combined and an observed response in common warts in vivo ***(Arch Virol et al., 2010).***

A study was done to evaluate systemic exposure, safety and tolerability of a combination of furosemide and digoxin after repeated topical application in subjects with common warts that were otherwise healthy ***(Gussekloo et al., 2015).***

In addition, exploratory pharmacodynamic effects on wart morphology and HPV load were included ***(Assen et al., 2017).***

Aim of the Work

To verify the efficacy, safety and tolerability of a topical formula composed of furosemide and digoxin in the treatment of multiple resistant common warts.

REVIEW OF LITERATURE

Warts

Warts are benign proliferations of the skin and mucosa that result from infection with HPV ***(Vali and Ferdowsi, 2007).*** They are usually classified according to their clinical location and morphology into three categories: cutaneous, anogenital, and extracutaneous papillomavirues infections ***(Filippone, 2014).***

Warts have their own blood and nerve supply. Commonly, pinpoint black areas are visible on the warts surface. These black dots are the wart's superficial network of capillaries, but may only be visible after the top layer of callus tissue is removed ***(Laube, 2014).***

Prevalence of warts

Although the prevalence of common warts in general population is unknown, warts occur in approximately 5% to 20% of children and young adults ***(Wiley et al., 2012).***

Approximately 23% of warts regress spontaneously within 2 months, 30% within 3 months and 65% to 78% within 2 years ***(Sterling et al., 2011).*** Previously infected patients have a higher risk for development of new warts than those never infected ***(Allenand Siegfried, 2009).***