Exploring the use of Ingenol Mebutate to prevent non-melanoma skin cancer: a review

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A thesis submitted to the School of Pharmacy in partial fulfillment of the requirements for the degree of Bachelor of Pharmacy (Hons.)

Department of Pharmacy
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September, 2022

Declaration

It is hereby declared that

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2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
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Approval

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Ethics Statement

This study does not involve any kind of animal or human trial.

Abstract

Globally, the incidence of non-melanoma skin cancer is increasing rapidly. Actinic keratosis (AK) is a type of sun damaged skin disease with a greater probability of turning into squamous cell cancer. However it is difficult to determine which AK will progress to SCC, although the presence of AK is an indication of SCC risk. Moreover, surgical excision is the major therapy, the innovative therapeutic agents has been prompted by the increase in patient desire for efficient, tissue-preserving methods with superior therapeutic results. In this context, Ingenol mebutate is an innovative skin treatment with immunostimulatory and chemoablative properties. It is derived from the plastic sap of the plant Euphorbia peplus, which is known for its ability to kill cancer cells. Clinical trials have shown Ingenol mebutate is safe and effective, prompting the FDA to approve this chemotherapeutic specialist for AK treatment in 2012. Recent effective experts for AK field therapy should be used for a long period, whereas ingenol should be used for three days. Ingenol is another useful option that is favorable, safe, feasible, sufficient, and long-lasting. The present review provides a comprehensive overview about the current use and future prospects of Ingenol mebutate as a potential treatment option to treat non-melanoma skin cancer, specifically AK. The current review covers the mechanism of action and preclinical studies of Ingenol mebutate with a particular focus on the clinical studies that warrant the safety and efficacy of Ingenol mebutate for the treatment of AK.

Keywords: Non-melanoma skin cancer, actinic keratosis, squamous cell carcinoma, ingenol mebutate.

Dedication

Dedicated to my Beloved Parents & Respected Faculty Members

Acknowledgement

To start, I would like to thank Almighty Allah (SWT) for keeping me healthy and safe during the project, which made it possible to finish on time.

I would like to express my heartiest gratitude to my respected supervisor. (Dr. Zara Sheikh, Assistant Professor, School of Pharmacy, Brac University), for giving me the chance to work on this project, which has also provided me with the opportunity to do a lot of research and learn a lot of new things. I will always be grateful to her for being so patient and giving me all of that expert, helpful, and sincere advice throughout this whole study.

Also, I would also like to express my cordial gratitude to our honorable Dean, Professor Dr. Eva Rahman Kabir Madam and the whole faculty members for her guidance, help and support throughout the last four years of my bachelors in department of pharmacy which will definitely help me in the future while pursuing my dream.

Finally, I would like to thank everyone involved from the bottom of my heart for their helpful cooperation in this regard.

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List of Acronyms

AK: Actinic keratosis

BCCs: Basal Cell Carcinomas

CP: Clobetasol Propionate

DFMO: Difluromethylornithine

HPV: Human Papilloma Virus

IngMeb: Ingenol Mebutate

NMSC: Non-melanoma Skin Cancer

PDT: Photodynamic Therapy

PKC: Protein Kinase C

SCCs: Squamous Cell Carcinomas

TNF: Tumor Necrosis Factor

UV: Ultra Violet

UVR: Ultra Violet Radiation

CHAPTER 1

INTRODUCTION

1.1 Background

Non-melanoma skin cancer (NMSC) that includes mostly basal cell carcinomas (BCCs) and squamous cell carcinomas (SCCs) are most common cancers among Caucasians with fair skin (Bray et al., 2018; Samarasinghe & Madan, 2012) .The occurrence of NMSC has increased, and it is estimated that between two and three million new cases are identified on a worldwide scale every year. The highest rates have been seen in the equatorial region, such as in the northern regions of Australia (Samarasinghe & Madan, 2012). In Australia, clinical care of squamous cell carcinomas and basal cell carcinomas accounted for almost 8.1 percent of cancer expenditure in the Australian health system in 2008-2009 (Excluding screening) (Aihw, n.d.). The prevalence of NMSC is much lower in the Asian sub-continent compared to what has been observed in western world. Squamous cell cancer is usual occurs skin cancer in India even though NMSC is uncommon in Asian nations (Panda, 2010). However, the actual incidence in India has not been recorded in the literature (Aditya & Gupta, 2013; Panda, 2010). Clinical dermatologists in India believe that NMSC occupies a limited region due to the apparently protective characteristics with increased eumelanin present in brown Indian people. According to study, Indians have a wide range of cases, including unusual types of NMSC (Aditya & Gupta, 2013; Panda, 2010).

The major risk factor for skin cancer is UV radiation emitted by sunshine. In spite of the rising public awareness about the hazards of direct sunlight, the prevalence of skin cancer is keeping on increasing at a rapid rate. The causes for tumor rise could be attributed to late diagnosis, an older population and increased exposure to UV radiation owing to ozone depletion, family history of

atypical moles, tobacco smoking (Chang et al., 2010; Cozzi et al., 2012; Norval et al., 2007). Sunlight, especially UVB, has the capacity to directly damage DNA and may operate both as a tumor initiator and a tumor promoter (Madan et al., 2010; Rass & Reichrath, n.d.). Other reasons of NMSC include occupational radiation and arsenic exposure, immunosuppression due to side effects of medication and HIV infection, chronic wounds, genetic disorder for example basal cell nevus disorder and HPV infection (Aditya & Gupta, 2013). White skin, brown hair, blue color of eyes, more melanocytic naevi, and the type 1 of Fitzpatrick skin are all phenotypic traits related with a significantly increased risk of these types of cancers (Aditya & Gupta, 2013; Samarasinghe & Madan, 2012).

Around 60% of SCC cases begin with actinic keratosis, which includes about 97% of all SCC cases that appear after exposure to sun on sun damaged skin (Aditya & Gupta, 2013). Actinic Keratosis is known as the intra-epidermal symptoms of UV induced keratinocyte neoplasia. UV B promotes thymidine dimer production in DNA which can lead to clonal proliferation and SCC. Since it is difficult to determine AK which may develop into skin cancer, the early detection of cancer and the treatment is quite necessary. NMSCs have a low relative mortality (0.1%), but they can cause severe morbidity, especially in prominent locations like the head and neck, leading to poor cosmetic results and expensive direct and indirect care expenses. While most NMSCs (excluding Merkel cell carcinoma) have a lower death rate than melanoma (Aihw, n.d.) mortality rates for SCC are greater when identified at a later stage (Eigentler et al., 2017; Gershenwald et al., 2017). Larger tumors or those with high-risk characteristics have a greater recurrence and metastasis rate for BCC and SCC. Small, simple tumors can be treated with cryotherapy, cautery, curettage, or excision. However, more advanced malignancies may require reconstructive surgery, radiation, chemotherapy, or immunotherapy (Aihw, n.d.; Migden et al., 2018). Potential screening

or treatment advantages should be weighed against healthcare hazards and economic expenses, including biopsies and surgery, to identify the optimal use of limited healthcare resources. This is especially true for NMSCs with low mortality rates, as advantages are likely to be reflected in increased quality of life.

1.2 Rationale and Aim of the Review

The treatment depends on variables including the location of the tumor, the patient's age at the diagnosis time, the severity of the illness, and whether or not the afflicted area has been treated in the past. Within the treatment region, the goal of field directed therapy is remove both clinically visible lesions and subclinical disorders. Surgical treatments include Mohs micrographic surgery, cryosurgery, regular excision, desiccation and curettage, radiation, phototherapy, and pharmaceutical drugs include imiquimod, retinoid, interferon, 5 fluorouracil and diclofenac are now available for the treatment of NMSC. These procedures have disadvantages in treatment safety or efficacy, convenience, patients' compliance or expense. The procedure is painful and may leave scars. Cryotherapy is an example of a lesion-directed therapeutic method that cannot treat a continuous region (field treatment). In addition, cryotherapy may be rather unpleasant, and patients frequently have hypopigmentation at the area where the liquid nitrogen was applied to their skin. The effectiveness of a curettage procedure depends on the expertise of the surgeon performing the procedure; hence it is only recommended for patients with a minimal risk of complications. Long-term therapy with topical medicines such as 5-fluorouracil and imiquimod leads to persistent local responses including unpleasant skin irritation, which in turn leads to non-compliance (Berman et al., 2010; Goldenberg et al., 2011; Lebwohl & Sohn, 2012). Innovative, non-invasive drugs that target crucial cellular receptors or immune responses have been developed to deliver non-surgical, tissue-sparing therapy with great visual results.

Therefore, this review aims to provide a comprehensive overview about the recent use and future prospects of Ingenol mebutate as a potential treatment option to treat non-melanoma skin cancer, specifically AK. The current review covers the mechanism of action and preclinical studies of Ingenol mebutate with a particular focus on the clinical studies that warrant the safety and efficacy of Ingenol mebutate for the treatment of AK.

1.3 Methodology

A thorough review of the current literature exploring the effectiveness of ingenol mebutate in preventing non-melanoma skin cancer especially AK, was carried by searching a vast number of current and well-known research studies and international peer-reviewed articles using PubMed, Google Scholar, Elsevier, Science Direct, Springer, and Cancer Registry webpages. The key words/phrases to search the papers used were ingenol mebutate, non-melanoma skin cancer, basal cell carcinoma diagnosis, squamous cell carcinoma, cancer prevention, clinical trials. Approximately 50 papers were selected for the review, to include pertinent data and information, with appropriate citation using Mendeley Library to present a comprehensive review on the use of Ingenol Mebutate for treatment of Actinic Keratosis.

CHAPTER 2

Current treatment of Non-melonoma skin cancer (NMSC)

A number of factors including disease stage, age at diagnosis, the location of the tumor, and previous treatments for the affected area all affect the course of treatment. In the treatment region, field-directed therapy has been widely used to remove both clinically obvious lesions and subclinical lesions. NMSC cancers are frequently numerous and recurrent due to the field-effect of UVR. Moh's surgery, surgical excision, and radiotherapy are among the treatments available, while imiquimod, photodynamic therapy and 5-fluorouracil may be used to treat superficial BCCs (Bonerandi et al., 2011; Madan et al., 2010). These techniques have one or more disadvantages in terms of treatment efficacy, safety, convenience, cosmetic outcome, patient's compliance and expense. Surgical removal is uncomfortable and may leave scars. Surgical and radiotherapy therapies can be disfiguring and cause functional impairment, particularly in patients with numerous tumors; consequently, prevention is a crucial element of NMSC management. Pathogenesis of most carcinomas is complex, involving several genetic and environmental variables. UV-induced NMSC is primarily determined by exposure and sensitivity to UVR, making it highly avoidable (Stratton et al., n.d.). Preventive methods include both primary and secondary chemoprevention to either prevent or reverse UV-damage progression.

The primary prevention of NMSC focuses on limiting UVR exposure. Preventive attempts have been made to inform the public about the significance of minimizing UVR exposure, such as avoiding midday sunlight exposure, using sunscreen, and using tanning beds sparingly. Despite such efforts, the incidence of AKs and NMSC continues to rise, necessitating the development of effective secondary, chemopreventive methods (Einspahr et al., 2002; Lomas et al., 2012).

Several systemic chemopreventive medications, including retinoids, nonsteroidal anti-inflammatory medicines, and difluoromethylornithine (DFMO), have been obseved to help patient avoid the development of AKs and NMSC (Chen et al., 2013; Einspahr et al., 2002; Soltani-Arabshahi & Tristani-Firouzi, 2013; Stratton et al., n.d.). Nicotinomide is another systemic chemopreventive medication with minor adverse effects that has shown potential in the treatment of NMSC in immune-competent low-risk individuals (Surjana et al., 2012). Topical formulations including retinoids, DFMO, and T4 Endonuclease V have been investigated, however since they require daily application, such therapies are inconvenient in reality. Still, DNA repair enzymes like T4 Endonuclease may be useful as a supplement to sunscreen in high-risk patients (Krutmann et al., 2015). Recent investigations have focused on topical therapies that need less frequent application, and multiple *in-vivo* studies have shown that PDT successfully inhibits carcinogenesis in mice (Togsverd-Bo et al., 2010). Despite the fact that existing clinical data is limited, PDT therapies in normal-appearing skin are an effective chemo preventative therapy in individuals at high risk, according to early data from an ongoing clinical investigation (Togsverd-Bo et al., 2015). It is still debatable whether active therapy is necessary for people with clinical photo damage and AKs. Lesion-directed, physically damaging cryotherapy is one of the most often utilized therapies for AKs (Es et al., n.d.). However, accumulating research suggests that AKs should not be seen as a syndrome isolated to particular lesions, but rather as a biomarker indicating of major underlying photodamage (Gupta et al., 2012). To prevent the development of NMSC, current AK therapies are shifting toward field-directed treatments, in which the therapeutic aim includes the surrounding subclinical field cencerizaion (Ulrich et al., 2010). Photodynamic therapy (PDT) and topical pharmaceutical treatments such as 5-fluorouracil (5-FU), diclofenac, imiquimod, and ingenol

mebutate are currently accessible field-directed therapies (Gupta et al., 2012; Lebwohl et al., n.d.; Swanson et al., 2010; Szeimies et al., 2002).

CHAPTER 3

Ingenol Mebutate: A novel topical drug for actinic keratosis

3.1 Overview of Ingenol Mebutate

The primary source of Ingenol mebulateis the extract from a plant called *Eurphorbia peplus* which is known as little spurge, milkweed, or radium weed (Aditya & Gupta, 2013). The chemical structure of this compound is basically a hydrophobic macrocyclic diterpene ester with a molecular formula $C_{25}H_{34}O_6$ and a molecular weight of 430.5 (Figure 1) (Aditya & Gupta, 2013). It is the oldest and most important group of plants used for medicine (Appendino & Szallasi, 1997). Euphorbiaceae is one of the largest flowering plant families, with over 3000 species in 200 genera. All euphorbias have a natural irritant in their latex that has been used as medicine since the beginning of time (Appendino & Szallasi, 1997). In 1986, a random sample of about 2,000 people living in Nambour, Australia, found that 164 of them treated their own skin cancers and AKs (Green & Beardmore Brisbane, n.d.). A clinical study found that using this sap three times daily significantly improved the appearance of 48 lesions, including SCCs, BCCs and intraepidermal carcinomas. After an average of 15 months follow up, (Berman, 2012), the full clinical elimination of more than fifty percent of lesions supported the clinical improvement of these lesions with the use of ingenol mebutate, thus signifying the potential of ingenol mebutate for the treatment of AK (Ramsay et al., 2011). Ingenol mebutate is available as a propyl alcohol-based gel formulation for topically use. Ingenol mebutate gel applied on the scalp and face once every three days at a dose of 0.015 percent, or to the body once every two days at a dose of 0.05 percent. These are two concentrations of the gel commercially available (PICATO is the marketed product of ingenol mebutate gel) (Aditya & Gupta, 2013) .

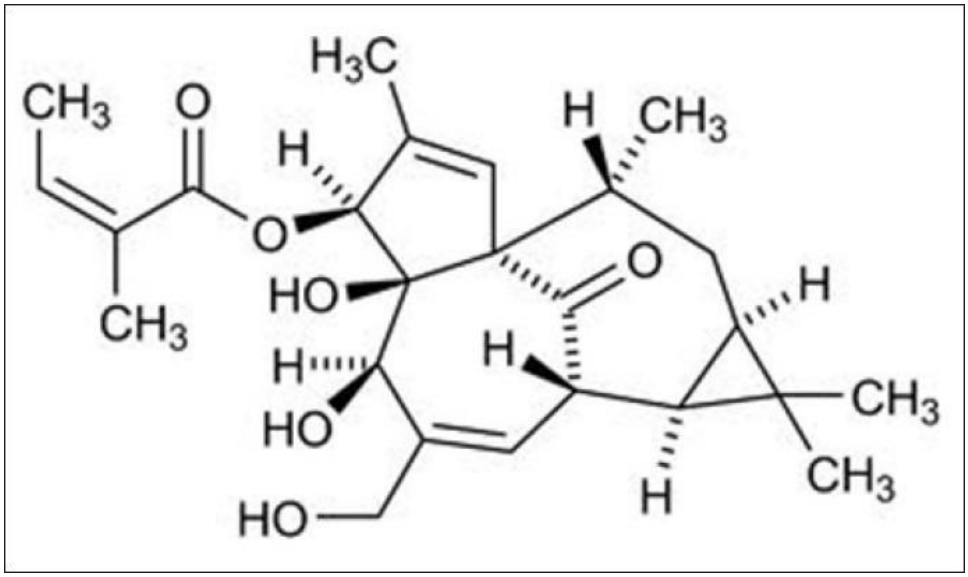

Figure 1: *Structure of Ingenol Mebutate (Aditya & Gupta, 2013).*

3.2 Mechanism of action

P-glycoproteins are responsible for the absorptive transport of topical ingenol mebutate, which allows it to penetrate through stratum corneum membrane and act in the dermis and hypodermis (Aditya & Gupta, 2013). Both the direct impact of the medicine and the generation of inflammatory cytokines at the site of the tumor are responsible for the first tumor ablation (Kindem et al., 2015; Lebwohl & Sohn, 2012). Primary necrosis is the first stage of cell death and is characterized by the fast rupture of the plasma membrane and subsequent enlargement of the mitochondria. In the next stage, neutrophil infiltration causes a localized acute inflammatory response. In the last phase, tumor-reactive antibodies are produced, and relapses are prevented by antibody-dependent neutrophil cytotoxicity, which eliminates any remaining cancer cells (Aditya & Gupta, 2013).

Furthermore, ingenol mebutate is an activator of the protein kinase C pathway which specifically target as well as disrupt the sub-epidermal intrinsic vasculature of tumors. Many undifferentiated cell lines respond to PKC delta activation by slowing cell proliferation, promoting cell cycle arrest, and facilitating differentiation. In addition to this, it induces the caspases in the cell to undergo apoptosis, adds stability to p53, and it induces the phosphorylation of signaling molecules (Ersvaer et al., 2010; R. H. Rosen et al., 2012).

3.3 Side Effects

Acute inflammation caused by Ingenol Mebutate usually appears on the skin as erythema, flaking, swelling, crusting, ulceration and vesiculation (R. Rosen et al., 2014). Most of the time, these responses last 14 days (about 2 weeks) (Medical & Med, 2017), with a peak on day 4. During this time, pain and itching are the most common side effects (Lebwohl et al., n.d.). For each patient, the extent of LSR may be difficult to predict, and some patients may have painful inflammation. It is presently unclear if the inflammatory response is necessary for attaining optimum treatment response or whether it is just an unpleasant reaction. However, it is essential that side effects could be reduced to a minimum when the therapy is being used for preventative purposes (Medical & Med, 2017).

In earlier research on mice, the neutrophil invasion generated by Ingenol Mebutate was prevented by the topical application of the strong glucocorticoid dexamethasone (Medical & Med, 2017). As a result, glucocorticoids have the potential to be used in the treatment of inflammation and adverse effects caused by this drug (Cronstein et al., 1992; Li et al., 2010). Clobetasol propionate is a glucocorticoid that can used topically on the skin to suppress the immune system, reduce inflammation, and vasoconstricting properties (Medical & Med, 2017). CP may alleviate IngMeb-

induced LSR, pain, and pruritus, but it is unclear whether this may reduce IngMeb's therapeutic impact (Li et al., 2010; Ogbourne Melanie Morris et al., 2006).

3.4 Inflammatory effects of Ingenol Mebutate

The inflammatory processes that eliminate AK are facilitated by low-dose ingenol mebutate's stimulation on protein kinase C delta. In various tumor cell lines, apoptosis may be induced by the drug ingenol mebutate by activating the protein kinase C (PKC) and moving it from the cytoplasm to the nucleus (Hampson et al., 2005; Kedei et al., 2004). Additionally, the synthesis and inflammatory cytokines secretion such as interleukin are included among the immunostimulatory effects of ingenol mebutate-mediated PKC activation (Kedei et al., 2004).Ingenol mebutate applied topically to mouse skin cancer tumors induced a neutrophil-rich inflammatory infiltration within hours(Ogbourne Melanie Morris et al., 2006a). When it comes to preventing tumor recurrence, Foxn1nu mice really need to maintain a normal neutrophil response (Ogbourne Melanie Morris et al., 2006a). Eliminating neutrophil activity in one model as well as another, the CD18-deficient animal, resulted in reduced inflammation and an increase in the incidence of tumor recurrence (0.70%) over a period of many weeks (Ogbourne Melanie Morris et al., 2006a). It's possible that the capacity of ingenol mebutate to penetrate the dermis will assist eradicate cancerous cells (Li et al., 2010). By binding to P-glycoprotein, ingenol mebutate works as a transport substrate and is thereby transferred to subepidermal areas (Li et al., 2010).

Ingenol mebutate induced fast inflammation was related with in vivo increase of interleukin-1, macrophage inflammatory protein-2 tumor necrosis factor-alpha (TNF) i.e., proinflammatory cytokines present in mouse skin which promote neutrophil recruitment and activation (Ogbourne Melanie Morris et al., 2006). In vitro investigations revealed that ingenol mebutate stimulated the production of interleukin-8, in normal human keratinocytes, the human version of macrophage

inflammatory protein-2, fibroblasts, neutrophils, and melanoma cells, as well as TNF- in keratinocytes (Ogbourne Melanie Morris et al., 2006). Ingenol mebutate stimulated keratinocytes' TNF- secretion. Separately, TNF- induced death ligand–mediated apoptosis in SCCs cell lines treated with diclofenac (Fecker et al., 2010). Ingenol mebutate–dependent TNF- stimulation may kill adjacent squamous cell carcinoma cells by activating death receptor pathways. Neutrophils are recruited to areas of inflammation by migrating through the vascular endothelial cells that line the postcapillary venules. Neutrophils were drawn to endothelial cells as a result of ingenol mebutate's increased cytokine production at the site of action (Ogbourne Melanie Morris et al., 2006). Besides this paracrine pathway, ingenol mebutate appears to stimulate endothelial cells directly via a PKC-dependent mechanism, enhancing neutrophil recruitment. Intercellular adhesion molecule 1, E-selecting and neutrophil chemoattractant interleukin-8 were all dose-dependently upregulated in endothelial cells after ingenol mebutate treatment. Because of ingenol mebutate's potential to activate several isoforms of protein kinase C, researchers examined into the significance of protein kinase C activation in endothelial cells (Kedei et al., 2004). According to stimulated protein kinase C isoenzyme expression, siRNA suppression testing and Western blot protein studies, ingenol mebutate directly activates PKC in endothelial cells to recruit neutrophils. The immune activation effects are illustrated in Figure 2.

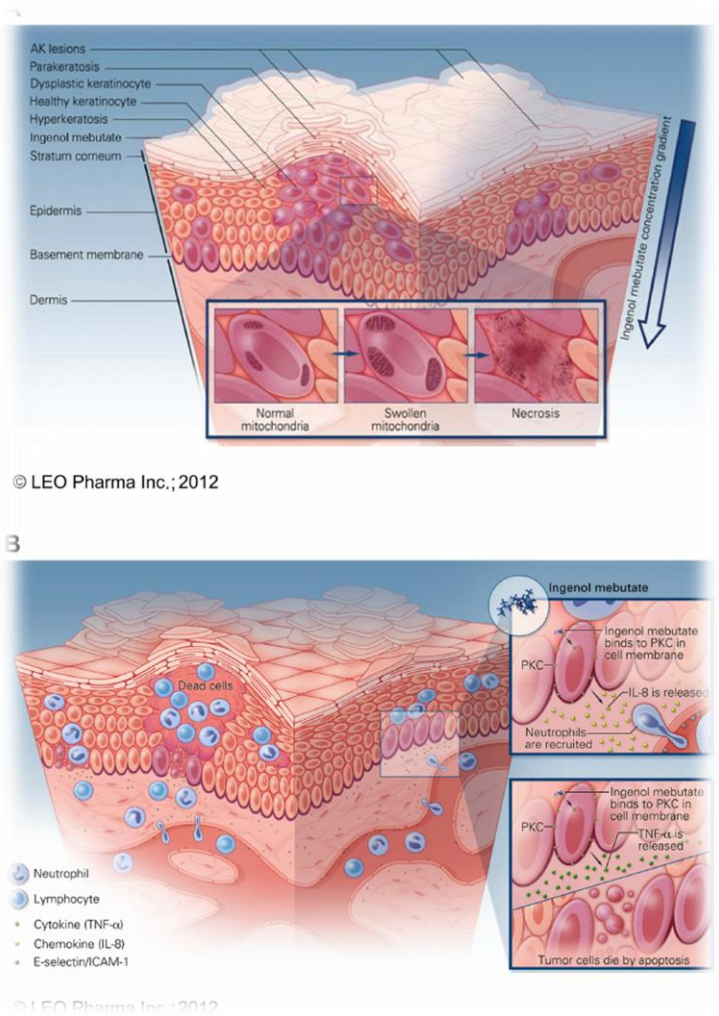

***Figure* 2** *: A schematic representation of hypothesized pathways using ingenol mebutate (Berman, 2012).*

Mouse tests show that antibody-dependent cellular cytotoxicity may help neutrophils destroy tumor cells. First, in SCID mice without a humoral immune response, ingenol mebutate-treated tumors relapsed often (Ogbourne Melanie Morris et al., 2006). Ingenol mebutate increases the development of anticancer antibodies in tumor-bearing mice, but not in untreated animals (Ogbourne Melanie Morris et al., 2006). Third observation suggesting the role of antibody-dependent cellular cytotoxicity in the prevention of relapse, and it is based on the ability of

antiserum from tumor-bearing Foxn1nu mice treated with ingenol mebutate to reduce the viability of LK tumor cells in vitro in the presence of murine neutrophils. (Ogbourne Melanie Morris et al., 2006a). It should be emphasized that these findings were performed in a murine model, and the existence and role of antibody-dependent cytotoxicity in the clearance of AKs from human skin is unclear.

3.5 Clinical studies on efficacy of Ingenol Mebutate

3.5.1 Phase 2a study

Siller et al. conducted a Phase 2a study on 58 patients with biopsy-confirmed AK of the arms, shoulders, face, chest or scalp that was randomly assigned, double-blind, and vehicle-controlled (Siller et al., 2009). On days 1 and 2 of the arm A study, five preselected lesions received treatment with 0.0025%, 0.01%, 0.05%, or vehicle gel. On days 1 and 8 of the arm B study, the same five lesions received treatment. Since the two application regimens had similar effectiveness and safety, the results were averaged. At day 85, the ingenol mebutate 0.05% therapy had the maximum rates of clinical lesion clearance, with full elimination of 71% of treated lesions; 67% of patients attained more than or equal to 80 percent clinical clearance of their lesions. Clinical lesion clearance rates were lowest in the vehicle therapy (Siller et al., 2009). For the ingenol mebutate 0.05% group, the most frequently reported local skin responses were erythema, dryness on 87%, and scars tissue on 67%. Eight individuals had a severe local skin response; however, most patients had a mild or moderate reaction. Apart from some scabbing that was still present on day 30, all local skin responses disappeared by the conclusion of the trial utill day 85 (Siller et al., 2009).

3.5.2 Phase 2b study

Ingenol mebutate gel was evaluated by Anderson et al. for the treatment of non-facial AKs in a Phase 2b study that included 222 patients. The trial was randomly assigned, double-blind, double-dummy, and controlled by a vehicle (Anderson et al., 2009). While using a concentration of 0.025% ingenol mebutate gel, it was used for three consecutive days; when using a concentration of 0.05%, it was applied for two or three consecutive days. Patients exhibited 4-8 AKs in a 25-centimeter square area. Most of the spots were on the arm around 66.2%, followed by the scalp around 27.5% and the rest were on the back, shoulder as well as chest. Skin and side effects were evaluated on days 3, 8, 15, 29, and 57. The main measure of how well the treatment worked was the percentage of patients whose levels of AKs dropped by at least 75% from their starting levels at 57 days (about 2 months). Clearance from baseline is the percentage of patients who no longer have any AKs, and AK reduction from baseline lesions is the same as the complete clearance rate.

On every measure of effectiveness, the three active treatments outperformed the vehicle, and the benefits of the therapies increased with increasing doses. Seventy-five percent, sixty-one percent, and fifty-six percent of patients in the different cohorts, respectively, achieved the main goal of more than or equal to 75 percent decrease of AKs compared to baseline. As predicted by ingenol mebutate's mechanism of action, local skin responses were most strong during 3 and 8 days. On day 8, flaking and erythema were present in as many as 96% of individuals. Local skin responses caused by all three main treatments resolved on their own within two to four weeks. There were no patients who dropped out of the trial owing to adverse events. During the research, there was no evidence of treatment related scarring and significant side effect of medicine. Ingenol mebutate was rated better for healing time, outcome of cosmetics, comparability with past AK treatments, and satisfaction levels (Anderson et al., 2009). The Phase-2 trials demonstrate the efficacy and

tolerability of a short course of topical ingenol mebutate gel for the treatment of AK. Those findings provided evidence to proceed with broader Phase 3 investigations of this drug.

3.5.3 Phase 3 study

In Phase 3 trials that were multicenter, randomized, double-blind, and controlled with vehicles, the effectiveness of ingenol mebutate as a therapy for AK was investigated (Lebwohl et al., n.d.). Two studies with a total of 547 participants each investigated the effects of applying ingenol mebutate 0.015% gel versus vehicle gel to AKs on the face or scalp for a period of three days, and two studies with a total of 458 participants each investigated the effects of applying ingenol mebutate 0.05% gel compared with vehicle gel to AKs on the arms and legs for a period of two days. Patients who had hypertrophic lesions or lesions that were resistant to treatment were not considered. According to the guidelines for the research, participants were not allowed to have recently used any suppressing medicines, cytotoxic agents, other AK treatments which might potentially interfere with the therapeutic assessment. The typical patient was 65 years old; majority had Fitzpatrick types 1 and 2 skin over half had skin cancer; and 7.5% experienced cryosurgery previously. All patients were evaluated for adverse effects and local skin responses on day 1, day 3, day 4, day 8, day 15, day 29, and day 57. Partial clearance (defined as a 75% decrease in lesion count compared with baseline) and percentage change from baseline in the total number of AKs were also included in the evaluation of AK clearance on day 57, in addition to the main goal of full elimination of all visible lesions. All ingenol mebutate group participants used the whole course of treatment (Lebwohl et al., n.d.).

CHAPTER 4

Summary with Future perspectives

The most frequent kind of skin cancer in humans is NMC. Increased outdoor activity, sun exposure, and changing clothing patterns contribute to the rising prevalence of skin cancer in North America. Surgical therapy is well known as conventional treatment, but patients want non-invasive options that can get rid of their lesions. There is still a need for treatment of pre-existing lesions despite the growing knowledge of the importance of prevention, such as sun protection through suitable clothing and the use of sunscreen. Actinic keratosis can manifest as a lesion or extend over a large area of skin. Squamous cell carcinomas can develop from these lesions, although the risk for individual lesions cannot be clinically differentiated. This suggests that actinic keratosis should also be actively managed in conjunction to BCCs, SCCs and intraepidermal carcinomas. In the treatment of superficial basal cell carcinoma and actinic keratosis, many studies have been conducted on the effectiveness as well as safety of using topical ingenol mebutate gel, which is a derivative of the plant Euphorbia peplus. The history of this new medicine, its mechanism of action and the current trial data for it may help clinicians advise patients on available treatment alternatives and choose the optimal therapy.

AK is a prevalent sun-damaged skin disorder that is significantly higher chances of SCCs. Even though the probability of a single lesion having turned into SCC each year is minimal, most people with sun damage to their skin have many lesions, which increase their chances up to 10 percent of extensive squamous cell carcinoma over a period of 10 years (Berman, 2012). Lesion-directed and field-directed approaches are used in the management of AK, with often various approaches being chosen on the basis nature of the lesions, the extent of sun exposure as well as the patient's

tolerance for therapy (Berman, 2012). Ingenol mebutate is a potential field therapy that can be put on the skin to treat this common, long-lasting skin condition. Ingenol mebutate gel is used to treat AK lesions by causing specific lesioned cell death and an immune response (Berman, 2012). Though, the exact way it works is not fully understood and is still being studied. Ingenol mebutate's clearance rates after two- or three-day treatment methods are competitive with those of other treatments which take longer treatment durations (Hanke et al., 2010; Loven et al., n.d.; Swanson et al., 2010; Wolf et al., n.d.). Moreover, it was observed that a 4-week of 5-fluorouracil therapy regimen resulted in a 43 percent full clearance rate (Loven et al., n.d.). Full clearance rates were from 25.0% to 35.6% with imiquimod 2.5% and 3.75% therapy after two week or three week treatment periods separated by an equal-length interval of without treatment (Swanson et al., 2010). Ingenol mebutate has short treatment duration and usually produce mild or moderate local skin responses. This may help AK patient who have difficulty adjusting to long duration of treatment courses to choose for shorter ones (Berman, 2012). Ingenol mebutate gel is extremely well tolerated, effective, and associated with near-perfect treatment adherence, according to clinical studies (Berman, 2012).

Therefore, additional research is required to determine the efficiency of glucocorticoids in reducing IngMeb-induced LSR, as well as the potential benefits of alternative treatments, such as nonsteroidal anti-inflammatory medicines (Medical & Med, 2017). Potentially, IngMeb prophylactic therapies in the future might enhance primary prevention initiatives aimed at decreasing the prevalence of NMSCs (Medical & Med, 2017). Although it has not been conclusively demonstrated, ingenol mebutate seems to be as effective as other non-surgical methods. The cosmetic benefits of its usage include its low toxicity, high patient tolerance, and positive cosmetic outcomes. Additionally, patients are more likely to choose the 2-3-day course of

therapy since it requires less time overall than other topical treatments already on the marketplace, which may improve adherence. To rigorously evaluate ingenol mebutate gel used for the prevention and treatment of actinic keratosis and non-melanoma skin cancer, further information is needed regarding its effectiveness and direct comparison to existing treatments. For longer-term clinical cure assurance, recurrence risk assessment, and clarity of safety data, longitudinal studies will be essential.

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