Evaluation of Serum Interleuken-10 & Interferon-γ in Patients with Multiple Warts after Treatment with BCG Vaccine

Thesis

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Shaimaa Taha

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List of Abbreviations

5-FU 5-Fluorouracil

AP1.....Activator Protein 1

APCs.....Antigen-Presenting Cells

BCG MRDJ .....BCG Moreau Rio De Janeiro

BCG.....Bacillus Calmette-Guérin

BMPs .....Bone Morphogenic Proteins

CIN .....Cervical Intraepithelial Neoplasia

CMI.....Cell Mediated Immunity

CPG .....Cytokine Phosphate Guarine

CREB.....CAMP Response Element binding protein

CSIF .....Cytokine Synthesis Inhibitory Factor

CTL.....Cytotoxic T Lymphocytes

DC .....Dendritic Cells

DCP .....Diphencyprone

DNCB.....Dinitrochlorobenzene

DPCP .....Diphenylcyclopropenone

DTH.....Delayed Type Hypersensitivity

DUSP1..... Dual Specifity phosphatase 1

E.....Early Viral Gene

ECM.....Extracellular Matrix

EGWs.....External Genital Warts

ERK.....Extracellular Signal Regulated Kinases

FC.....Fragment, Crystallizable

FOXP3.....Factor Forkhead Box P3

GM-CSF .....Granulocyte Monocyte Colony Stimulating Factor

List of Abbreviations

GSK ..... Glycogen Synthase Kinase

HPVs.....Human Papillomaviruses

HSCs.....Hematopoietic Stem Cells

HSIL .....High Grade Squamous Intraepithelial Lesion

HSPGs .....Heparan Sulfate Proteoglycans

IL-10.....Interleukin-10

ISGs.....Interferon Stimulated Genes

JAK .....Janus Activated Kinase

L .....Late Viral Gene

LC.....Langerhans cell

LCR .....Long Control Region

LSIL.....Low Grade Squamous Intraepithelial Lesion

MAPK .....Mitogen Activated Protein Kinase

MCP.....Monocyte Chemotactic Protein

MHC .....Major Histocompatibility Complex

MIP.....Macrophage Inflammatory Protein

NF-KB.....Nuclear Factor KB

NK .....Natural Killer

PCR .....Polymerase Chain Reaction

PI3K .....Phosphoinsitide 3 Kinase

PPD.....Purified Protein Derivative

PRPS .....Pattern Recognition Receptors

SADBE.....Squaric Acid Dibutylester

STAT3 .....Signal Transducer and Activator of Transcription 3

TB.....Tuberculosis

List of Abbreviations

TGF .....Transforming Growth Factor

TLR .....Toll-Like Receptor

TNF .....Tumor Necrosis Factor

TPL2.....Tumor Progression Locus 2

TPO .....Thrombopoietin

TST.....Tuberculin Skin Test

UNICEF.....United Nations Children's Fund

VLP.....Virus Like Particles

WHIM syndrome....Warts, Hypogamma globulinemia, Immunodifiency and Myelokathexis

WHO .....World Health Organization

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INTRODUCTION

Warts are benign epithelial neoplasms affecting the epithelium of the skin and mucous membranes that result from infection with human papillomavirus (HPV) ***(Yazdanfar et al., 2008).***

Common warts affect patients' quality of life by causing adverse psychological effects, also certain types of HPV may induce life-threatening malignancies ***(Rijkaart et al., 2012).*** HPV 16 has also been strongly associated with various head and neck cancers including head and neck squamous cell carcinoma and oropharyngeal carcinoma of the tonsils ***(Rautava et al., 2012).*** The incidence of HPV induced oral cancers appears to be increasing ***(Gaston and Garry, 2012).***

HPVs are the causative agents of a variety of benign and cancerous lesions of the skin and other epithelial surfaces. At least 189 HPV genotypes have been described ***(Gooi et al., 2016).***

Most HPV types are associated with one or a few histopathologically distinct types of lesions and may be restricted to a particular location on the body. HPV types 2, 4, 26, 29 and others are responsible for common warts (verruca vulgaris), which are slightly raised rough surface epithelial proliferations that occur most often on the hands, can also grow elsewhere on the body. Other types of warts include plantar warts (verruca plantaris) that occur most commonly on the soles of the feet (HPV 1 and others), flat warts (verruca plana) usually appearing on the face (HPV

3, 10, 38 and others), butcher's warts of the hands and fingers (HPV 7), oral and genital warts (condyloma acuminata; HPV 6, 11, 16, 18 and many others) ***(Gaston and Garry, 2012).***

BCG is a bacterial preparation of a strain called Bacillus-Calmette-Guerin. It contains live attenuated mycobacterium bovis that has lost its virulence in humans by being especially cultured in an artificial medium for years and was developed as a vaccine against tuberculosis ***(Fine et al., 1999).***

BCG was introduced as a prophylactic agent against tuberculosis (TB), accidentally it has been found that the leprosy incidence has decreased tremendously**.** The rationale of the use of BCG as a protective vaccine against leprosy rests on the assumption that cross reacting antigens exist between Mycobacterium leprae and BCG and that following BCG vaccination, protective immunity against leprosy will be developed **(Zodpey, 2007).**

The BCG also had been used in the treatment of malignant melanoma, transitional cell carcinoma of the bladder**,** in alopecia areata and recurrent oral aphthosis ***(Sharquie and Hayani, 2005).*** The percentage of skin disease among BCG vaccinated individuals was significantly lower compared with healthy individual controls and these diseases include psoriasis, fungal infection, cutaneous leishmaniasis, molluscum contagiosum and lichen planus indicating that BCG decreases the frequency of skin diseases ***(Sharquie et al., 2008).***

Patients with condyloma accuminata had shown an imbalance of Th1/Th2 cytokines production ***(Zuo et al., 2004)***. Th2 cells secrete IL-4 and IL-10 (and other cytokines) and help antigen-primed B lymphocytes differentiate into plasma cells and secrete antibodies; the effector molecules of humoral responses. Th1 cells secrete IFN-γ and create a milieu in which key cytotoxic effectors, macrophages, natural killer cells and cytotoxic CD8+ T lymphocytes are activated, generating cell mediated immunity ***(Rouse and Suvas, 2004).***

A lot of works attempted to prove the efficacy of BCG vaccine as an immunotherapy in warts and other immunomediated diseases whether by topical application ***(Metawea et al., 2005)***, intradermal administration ***(Sharquie et al., 2008)*** or intralesionally the study of ***Yuan et al. (2007)***.

The mechanism of action of BCG in the treatment of warts, could be explained on the basis of stimulating macrophages, T and B lymphocytes, natural killer cells function that might help in resolution of the viral warts ***(Sharquie et al., 2008).***

Aim of the Work

The aim of this work was to evaluate the level of serum IL-10, IFN-γ before and after multiple intradermal injections of BCG vaccine and to compare the levels in clinical responders versus non responders to evaluate its possible clinical efficacy in the treatment of warts.