A COMPARATIVE STUDY ON TREATMENT OF VITILIGO USING SYSTEMIC STEROIDS VERSUS COMBINED NB-UVB WITH SYSTEMIC STEROIDS

Thesis

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4-HA	4- Hydroxy Anisole
4-MP	4- Methoxyl Phenol
5-FU	5- Fluoro Uracil
ACTH	Adreno Cortico Tropic Hormone
ADCC	Antibody Dependent Cellular Cytotoxicity
AMA	Anti-Melanocyte Antibodies
ATF-2	Activating Transcription Factor-2
BAFF	B-Lymphocyte Activating Factor
BB-UVB	Broad Band Ultra Violet B
BER	Base Excision Repair
bFGF	Basic Fibroblast Growth Factor
BSA	Body Surface Area
CAT	Catalase
CTLA4	Cytotoxic T-Lymphocyte-Associated protein 4
CXCL	Chemokine ligand belonging to the CXC chemokine family
DHA	Dihydroxyacetone
DLQI	Dermatology Life Quality Index
DMSO	Di Methyl Sulphoxide
DNA	Deoxy Ribo Nucleic Acid
DOPA	Dihydroxy Phenyl Alanine
ELISA	Enzyme Linked Immunosorbent Assay
Er-YAG	Erbium- Yttrium Aluminum Garnet
ET-1	Endothelin -1
Fas	A receptor present in cells that binds with Fas ligand to induce apoptosis
FGF2	Fibroblast Growth Factor 2
FoxP3	ForkHead Box P3
GH	Growth Hormone

GM-CSF	Granulocyte Monocyte Colony Stimulating Factor
GPX	Glutathione Peroxidase
GSH-Px	Glutathione Peroxidase
GST	Glutathione S-Transferase
GV	Generalized Vitiligo
GWAS	Genome Wide Association Studies
H_2O_2	Hydrogen Peroxide
HGF	Hepatocyte Growth Factor
HLA	Human Leucocyte Antigen
HO-1	Heme Oxygenase-1
HSP	Heat Shock Protein
ICAM-1	Intra Cellular Adhesion Molecule-1
IFN-γ	Interferon Gamma
IGF-1	Insulin like Growth Factor 1
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IL	Interleukin
ILCS	Intra Lesional Corticosteroids
IV	Intra Venous
LFA-1	Lymphocyte Function Associated Antigen
MBEH	Mono Benzyl Ether of Hydroquinone
MCHR1	Melanin Concentrating Hormone Receptor 1
MDA	Malonyl Aldehyde
MEL	Monochromatic Excimer Light
MHC	Major Histocompatability Complex
miRNAs	Micro RNAs
Mitf	Microphthalmia-associated transcription factor
MMP	Melanosomal matrix protein
MMP2	Matrix Metallo Proteinase 2

MOP	Methoxypsoralen
MTT	3-(4,5-dimethyl-2-thiazolyl)-2, 5-diphenyl-2H-tetrazolium bromide
mRNA	Messenger Ribo Nucleic Acid
MTHFR	Methylene Tetra Hydro Folate Reductase
MxA	Human Myxovirus Resistance Protein 1
NB-UVB	Narrow Band Ultra Violet B
Nd-YAG	Neodymium-Yttrium Aluminium Garnet
NER	Nucleotide Excicsion Repair
NFAT	Nuclear factor of activated T-cells
NFκβ	Nuclear Factor Kappa Beta
NLR	Nucleotide-binding domain and leucine rich repeat containing
NLRP1	Pyrin domain containing protein 1
NQO1	NAD(P)H:Quinone Acceptor Oxidoreductase 1
Nrf-2	Nuclear factor-like 2
NSV	Non Segmental Vitiligo
OMP	Oral Mini Pulse
P53	Tumor suppressor protein 53
PAX3	Paired Box 3
PBS	Phosphate Buffered Saline
PCR	Polymerase Chain Reaction
pDC	Plasmacytoid Dendritic Cells
PG	Prostaglandin
PGE2	Prostaglandin E2
POMC	Pro Opio Melano Cortin
PRX	Peroxiredoxin
PUVA	Psoralen –Ultra Violet A
PUVAsol	PUVA plus sun light
ROS	Reactive Oxygen Species
SCF	Stem Cell Factor

SOD	Super Oxide Dismutase
STAT3	Signal Transducer and Activator of Transcription 3
SV	Segmental Vitiligo
TCI	TopicalCalcineurin Inhibitor
TCS	Topical Corticosteroids
TGF-β1	Transforming Growth Factor Beta 1
tHcy	Total Homocysteine
TH1	T Helper 1 lymphocytes
TNF-α	Tumor Necrosis Factor alpha
T-reg	Regulatory T cells
TRP	Tyrosinase Related Peptide
UCA	Urocanic Acid
USF-1	Upstreamtranscription factor 1
UVR	Ultra Violet Rays
VASI	Vitiligo Area Score Index
VETF	Vitiligo European Task Force
VGICC	Vitiligo Global Issues Consensus Conference
VIDA	Vitiligo Disease Activity Score
VIS	Visual Impact Scale
VitiQol	Vitiligo Quality of life
XeCl	Xenon Chloride
ZAG	Zinc alpha 2-glycoprotein
α-MSH	Alpha Melanocyte Stimulating Hormone

ABSTRACT

BACKGROUND: The pathogenesis of vitiligo is complex and not yet fully understood, but it is believed to involve a combination of autoimmune, genetic, and environmental factors. Classic treatment options for vitiligo include narrow band UVB and psoralens plus UVA (PUVA). Oral steroids have been tried and reported to be effective in the treatment of vitiligo.

AIM: To assess clinical efficacy of NB-UVB combined with oral steroids compared to oral steroids alone in treatment of stable vitiligo patients, as well as observe any relapse/rebound that may possibly occur following cessation of treatment.

METHODS: 30 patients with stable vitiligo randomized into 2 groups; group A received NB- UVB for 36 sessions with oral steroids, whilst group B received oral steroids alone for 3 months. Both groups were followed up for 3 months. Basic fibroblast growth factor (bFGF) (marker of regression) and intercellular adhesion molecule (ICAM 1) (marker of activity) tissue levels were measured by RT-PCR before and after treatment and after follow-up. Anti-melanocyte antibodies (AMA) (marker of activity) detection in patients' sera was done using cellular Eliza before and after treatment and after follow up.

RESULTS: Regarding clinical results, in group A, patients showed an improvement in the mean value of vitiligo area score index (VASI) score from 20.8± 10.6 before treatment to 12.6± 6.5 after treatment. Three patients showed minimal clinical relapse during the course of treatment and 3 during the follow-up period. On the other hand, in group B, patients showed negligible improvement in the mean value of VASI score from 14.0± 7.5 before treatment to 13.6± 7.6 after treatment. One patient showed clinical relapse during the treatment period and 2 during the follow- up period. PCR data revealed bFGF increase and ICAM 1 decrease during treatment which was significantly higher in group A than in group B. During follow-up period, group A showed a bFGF decrease which was significantly higher than that in group B and showed a non-significant increase in ICAM 1in both groups. AMA didn't show any significant changes in both groups.

CONCLUSION: Combined NB-UVB and oral mini pulse (OMP) showed clinical superiority over OMP alone in treating stable vitiligo patients. The expected higher relapse rate with steroids only was not seen, may be due to the minimal clinical response to start with and the relatively short follow up period.

KEYWORDS: Vitiligo, Steroids, NB-UVB, Basic Fibroblast Growth Factor, ICAM-1, Anti-melanocyte antibodies

INTRODUCTION

INTRODUCTION

Vitiligo is an acquired leukoderma that results from the loss of epidermal melanocytes, and is characterized by depigmented macules and patches of skin. Ancient Egyptian texts first described these depigmented macules more than 3,000 years ago ***(Millington and Levell, 2007)***. The term vitiligo was perhaps derived from the latin word 'vitelius' and used to describe the white flesh of calves, then the word 'vitiligo' was attributed to Celsus in his classic Latin book De Medicina in the first Century AD ***(Flabella, 2009)***. Having a high rate of prevalence of about 1 to 2 percent of the world's population, or 40 to 50 million people ***(Taieb** et al., **2013)***, vitiligo occurs in localized, generalized, or segmental patterns; and can run a rapidly progressive course or remain stationary ***(Mahmoud** et al., **2008).***

The pathogenesis of vitiligo is complex and still not yet fully understood, but it is believed to involve a combination of autoimmune, genetic, and environmental factors. The autoimmune hypothesis suggesting that antibodies develop against melanocyte surface antigen has gained much popularity. In addition, the neuro-chemical and self-destruct hypotheses have also gained general acceptance ***(Panja** et al., **2013).***

Basic fibroblast growth factor (bFGF); initially identified as a mitogen with prominent angiogenic properties, has been recognized as a multifunctional growth factor ***(National Center for Biotechnology Information, 2014a)***. Basic FGF deficiency could be one of the etiological factors in the pathogenesis of vitiligo ***(Nada** et al., **2012)***. Studies showed the effectiveness of bFGF in stimulating vitiligo repigmentation by inducing proliferation and migration of hair-follicle outer-root-sheath melanocytes into the depigmented epidermis ***(Dong** et al., **2012b)***. Narrow-band ultraviolet B (UVB) irradiation stimulated cultured keratinocytes to release a significant amount of basic fibroblast growth factor (bFGF) ***(Wu***

*et al., **2006)***. On the contrary though, other studies found high bFGF levels in vitiliginous skin-blister fluid as well as in their serum, raising possibility of its role in the pathogenesis of vitiligo ***(Ozdemir** et al., **2000)***.

Functional melanocytes in patients with vitiligo vulgaris disappear from involved skin by mechanisms that have not yet been identified. The anti-melanocyte antibodies (AMA) were found to play a particularly important part in the pathogenesis of vitiligo. Antibodies directed against melanocyte cell surface antigens are often demonstrated in the sera of vitiligo patients ***(Panja** et al., **2013)***. Auto antibodies against melanocytes may result from a genetic predisposition to immune dysregulation at the T cell level, or from an immune response to melanocyte antigens that can be aggravated by damaged pigment cells ***(Deo** et al., **2011)***. IgG anti-melanocyte antibodies were found to induce melanocyte damage *in vitro* by a complement-mediated mechanism and antibody-dependent cellular cytotoxicity and in vivo following the passive immunization of nude mice grafted with human skin. ***(Deo** et al., **2011)***.

Intracellular adhesion molecule-1 (ICAM1) is a cell surface glycoprotein which is typically expressed on endothelial cells and cells of the immune system. It binds to integrins of type CD11a / CD18, or CD11b/CD18. Intracellular adhesion molecule (ICAM-1) functions as a ligand for the lymphocyte function associated antigen-1 (LFA-1) ***(National Center for Biotechnology Information, 2014b)***. Various cell types, including vascular endothelial cells, lymphocytes, fibroblasts, tissue macrophages, keratinocytes and melanocytes are able to express ICAM-1. Increased expression of ICAM-1 in patients with vitiligo was reported, especially in cases with active disease and those with early age of onset ***(Laddha** et al., **2013).***