BROAD-BAND UVA VERSUS PUVA IN THE TREATMENT OF VITILIGO: A COMPARATIVE STUDY

Thesis

Submitted in Fulfillment of M.D Degree in Dermatology

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ABSTRACT

Background: Vitiligo is an acquired hypomelanotic disorder characterized by decrease Bcl2 (antiapoptotic marker) immunoexpression in melanocytes of vitiliginous lesions in untreated patients. The mainstay treatment for vitiligo is PUVA. BB-UVA was found to produce tanning of vitiliginous lesions.

Aim of work: To compare the efficacy of PUVA versus BB-UVA in the treatment of vitiligo and whether BB-UVA can be an alternative line of therapy. The study also aimed at comparing the effect of PUVA versus BB-UVA on the apoptosis of melanocytes and keratinocytes in vitiligo patients and whether prevention of apoptosis is a possible mechanism of clinical improvement.

Patients and Methods: This prospective randomized controlled single blinded comparative clinical trial included 45 patients with generalized vitiligo who were randomly divided into three equal groups (15 patients in each group); group A receiving UVA 15 J/cm^2/session, group B receiving UVA 10J/cm^2/session and group C receiving PUVA. The patients received three sessions/week for five months (60 sessions). Patients were evaluated clinically and by immunoexpression of Bcl2 in melanocytes and keratinocytes in skin biopsies.

Results: The extent of clinical response was significantly higher in patients receiving PUVA than the other two groups at mid therapy (30 sessions). At the end of the study (60 sessions), the clinical response was significantly higher in patients receiving PUVA than patients receiving UVA 10 J /cm^2 only. Phototoxic reactions were significantly higher in patients receiving PUVA. Immunoexpression of Bcl2 in melanocytes and keratinocytes was significantly higher at mid therapy than pre therapy in all the groups regardless of the type of therapy. Also, there was no significant correlation between the extent of response and the difference in Bcl2 immunoexpression pre and mid therapy in the three groups.

Conclusion: BB-UVA produces mainly tanning of the lesions, and only at higher doses the extent of response is comparable to PUVA. Irradiance of vitiliginous lesions by UVA, with or without psoralen intake, leads to antiapoptotic effect on melanocytes and keratinocytes. However, this effect does not correlate with the clinical improvement of vitiligo lesions.

Keywords: Vitiligo, PUVA, BB-UVA, Phototherapy and Bcl2.

LIST OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

ADCC:	Antibody-dependent cell-mediated cytotoxicity
AIF:	Apoptosis-inducing factor
BB-UVA:	Broad-band UVA
bFGF:	Basic fibroblast growth factor
Ca^{2+}:	Calcium
CBT:	Cognitive behavioural techniques
CLA:	Cutaneous lymphocyte-associated antigen
CTLs:	Cytotoxic T lymphocytes
DAB:	Diamino benzidine
DED:	Death effector domain
DISC:	Death-inducing signaling complex
DNA:	Deoxyribonucleic acid
DOPA:	Dihydroxyphenylalanine
DR6:	Death receptor 6
DT:	Delayed tanning
EGF:	Epidermal growth factor
EM:	Electron microscope
FADD:	Fas-associated death domain
GM-CSF:	Granulocyte macrophage colony stimulating factor
H_2O_2:	Hydrogen peroxide
HGF:	Hepatocyte growth factor
HLA-DR:	Human leucocyte antigen-DR
HRP:	Horseradish peroxidase
HRQL:	Health-related quality of life
ICAM-1:	Intercellular adhesion molecule-1
IFN-γ:	Interferon- γ
IKP:	Isomorphic koebner phenomenon

IL-10: Interleukin-10
IL-13: Interleukin-13
IL-17: Interleukin-17
IL-2: Interleukin-2
IL-4: Interleukin-4
IL-5: Interleukin-5
IL-6: Interleukin-6
IPD: Immediate pigment darkening
J/cm^2: Joules/centimeter square
KIT: Stem cell factor receptor
KUVA: Khellin plus UVA
LFA-1: Lymphocyte function associated antigen-1
MHC: Major histocompatibility complex
MITF: Microphthalmia associated transcription factor
MOP: Methoxypsoralen
mRNA: Messenger ribonucleic acid
NB-UVB: Narrow-band UVB
NGF: Nerve growth factor
PASI: Psoriasis area scoring index
PGE-2: Prostaglandin E2
PLE: Polymorphic light eruption
PUVA: Psoralen plus UVA
PUVB: Psoralen plus UVB
QOL: Quality of life
r^2: Correlation coefficient
RCM: Reflectance-mode confocal microscopy
RNA: Ribonucleic acid
ROS: Reactive oxygen species
SCF: Stem cell factor
SED: Suberythema Dose
TGF- β: Transforming growth factor – β

Th1: T helper 1

Th17: T helper 17

TMP: Trimethyl-psoralen

TNF-R1: Tumor necrosis factor receptor-1

TNF-β: Tumor necrosis factor-β

TRAIL-R1: Tumor necrosis factor related apoptosis inducing ligand receptor-1

TRAIL-R2: Tumor necrosis factor-related apoptosis–inducing ligand receptor-2

TRAMP: Tumor necrosis factor receptor- related apoptosis mediating protein

T-regs: Regulatory T-cells

TYRP1: Tyrosinase related protein 1

TYRP2: Tyrosinase related protein 2

UVR: Ultraviolet radiation

VASI: Vitiligo area scoring index

VETF: Vitiligo European task force

α-MSH: α -melanocyte stimulating hormone

$6BH_4$: 6-tetrahydrobiopterin

$7BH_4$: 7-tetrahydrobiopterin

Patient no.	Group no.	Age	Sex	Disease Duration	Disease activity	Range of body affection	Types of Response			Extent of response Mid therapy	Extent of response post therapy	Phototoxic reaction	Thickening	Koebner.	Bcl2pre	Bcl2post	Bcl2 diff.
							Perifollicular pigmentation(a)	Marginal pigmentation (b)	Tanning (c)								
1	uva15j(A)	13	m	7	-ve	30%	a	no	c	1	2	no	no	no	0.74	0.96	0.22
2	uva15j (A)	20	f	5	-ve	20%	a	no	c	1	2	no	no	no	1.1	1.1	0.0
3	uva10j (B)	17	f	10	+ve	70%	a	no	c	0	1	no	no	no	0.96	1.2	0.24
4	uva10j (B)	17	f	4	-ve	20%	a	b	no	0	2	no	no	no	1.13	1.22	0.09
5	uva10j (B)	19	f	14	+ve	50 %	no	no	no	0	0	no	no	no	0.78	0.78	0.0
6	Puva (C)	24	m	3	+ve	10 %	a	b	no	1	2	no	no	no	0.78	0.79	0.01
7	uva10j (B)	20	f	10	+ve	50 %	a	b	c	1	2	no	no	no	0.78	0.78	0.0
8	uva10j (B)	45	f	10	+ve	30 %	a	no	c	1	2	no	no	no	0.95	1.1	0.15
9	uva15j (A)	50	f	1.5	-ve	70 %	a	b	c	1	4	no	no	no	0.89	0.96	0.07
10	Puva (C)	28	f	5	+ve	80 %	a	no	no	1	2	p	no	no	0.88	0.99	0.11
11	Puva (C)	27	m	3	+ve	40 %	a	b	no	1	2	no	no	no	1	1.2	0.2
12	uva10j (B)	60	f	1	-ve	90%	a	no	c	1	1	p	no	no	0.72	0.77	0.05
13	uva15j (A)	19	f	3	+ve	10 %	no	no	c	1	1	no	no	no	0.76	1.07	0.31
14	Puva (C)	18	f	1	+ve	60 %	a	no	c	1	2	p	no	no	0.66	0.69	0.03

Patient no.	Group no.	Age	Sex	Disease Duration	Disease activity	Range of body affection	Types of Response			Extent of response Mid therapy	Extent of response post therapy	Phototoxic reaction	Thickening	Koebner.	Bcl2pre	Bcl2post	Bcl2 diff.
							Perifollicular pigmentation(a)	Marginal pigmentation (b)	Tanning (c)								
15	uva10j (B)	28	m	8	+ve	30 %	no	B	c	0	2	p	no	no	0.6	0.7	0.1
16	uva10j (B)	37	m	5	+ve	30 %	a	no	c	0	1	p	no	no	0.67	0.93	0.26
17	Puva (C)	55	m	20	+ve	10 %	a	no	no	1	2	p	no	no	0.75	0.89	0.14
18	uva15j (A)	13	f	10	+ve	30 %	a	no	c	1	2	p	no	no	0.84	1.01	0.17
19	uva10j (B)	45	f	4	+ve	80 %	a	no	no	1	1	p	no	no	0.83	0.83	0.0
20	Puva (C)	27	f	1	+ve	40 %	a	no	no	2	2	p	no	no	0.84	0.94	0.1
21	uva15j (A)	24	f	13	+ve	50 %	no	no	c	1	1	no	no	no	0.6	0.8	0.2
22	Puva (C)	40	f	20	-ve	50 %	a	no	no	2	3	no	t	no	0.65	0.75	0.1
23	uva15j (A)	30	f	3	+ve	30 %	no	no	c	1	2	p	no	no	0.49	0.86	0.37
24	uva15j (A)	18	f	1		10%								no			
25	Puva (C)	40	f	6	+ve	30 %	a	no	no	2	3	p	t	no	0.65	0.73	0.08
26	Puva (C)	20	f	15	+ve	20 %	a	no	no	1	2	p	t	no	0.81	0.85	0.04
27	uva15j (A)	30	m	0.5	+ve	20 %	no	no	c	1	1	no	no	no	0.61	0.65	0.04
28	uva15j (A)	13	f	6	+ve	30 %	no	b	c	1	1	no	no	no	0.49	0.71	0.22
29	uva10j(B)	37	f	20	+ve	20 %	no	no	c	1	1	p	no	no	0.94	1.14	0.2
30	uva15j (A)	23	f	6	+ve	20 %	no	b	c	1	1	no	no	no	0.65	0.85	0.2

Patient no.	Group no.	Age	Sex	Disease Duration	Disease activity	Range of body affection	Types of Response			Extent of response Mid therapy	Extent of response post therapy	Phototoxic reaction	Thickening	Koebner.	Bcl2pre	Bcl2post	Bcl2 diff.
							Perifollicular pigmentation(a)	Marginal pigmentation (b)	Tanning (c)								
31	uva10j (B)	21	f	10	-ve	20 %	no	no	c	1	1	no	no	no	0.8	0.93	0.13
32	Puva (C)	30	m	4		10%											
33	uva10j (B)	35	f	5		30%											
34	uva15j (A)	42	f	6	+ve	20 %	a	no	c	1	2	p	no	no	0.74	0.8	0.06
35	Puva (C)	21	m	11	-ve	10 %	a	no	no	1	2	no	no	no	0.74	0.8	0.06
36	Puva (C)	28	f	18	+ve	40 %	a	no	no	2	3	p	no	no	0.83	0.95	0.12
37	Uva10j (B)	40	f	15	+ve	30 %	no	no	c	0	1	no	t	no	0.77	0.83	0.06
38	Uva15j (A)	18	f	5	+ve	40 %	a	no	c	1	2	no	no	no	0.79	0.9	0.11
39	Uva10j (B)	13	f	4	+ve	60 %	no	no	c	0	1	no	no	no	0.7	0.8	0.1
40	Uva15j (A)	27	m	3	+ve	20 %	a	no	no	1	2	no	no	no	0.75	0.85	0.1
41	Puva (C)	26	m	1	-ve	30 %	a	no	no	1	2	no	no	no	0.65	0.74	0.09
42	Puva (C)	60	m	2		20%											
43	Puva (C)	40	m	2	-ve	20 %	a	no	no	1	2	p	no	no	0.78	0.85	0.07
44	Uva15j (A)	20	f	4	+ve	30 %	a	no	c	1	2	no	no	no	0.6	0.7	0.1
45	Uva10j (B)	40	f	2	-ve	30 %	no	no	c	0	1	no	no	no	0.65	0.7	0.05

INTRODUCTION

Vitiligo is an acquired hypomelanotic disorder characterized by circumscribed, depigmented macules in the skin resulting from loss of functional melanocytes (melanocytopenic) from the cutaneous epidermis (***Kemp et al., 2007***). Although, at first vitiligo might be viewed as a minor disorder, the impact on patients' self-esteem and social interactions can be devastating particularly in patients with deeply pigmented skin (***Kemp et al., 2001***).

On clinical basis, vitiligo is regarded as relatively easily diagnosed disease. However, on cellular basis the mechanisms that lead to the appearance of the depigmented macules is still uncertain. Various possible causes for the pathogenesis of vitiligo have been proposed including genetic, immune-mediated, auto-cytotoxic and neuronal ones (***Passeron and Ortonne, 2005 and Dell' Anna and Picardo, 2006***).

Over the last years, a bipolar approach has characterized the studies on the pathogenesis of vitiligo. One pole corresponds to an immune-mediated impairment of cells evidenced by the presence of circulating autoantibodies and autoreactive T-cells against pigment cell antigen (***Ongenae et al., 2003 and Le poole et al., 2004***). Whereas the other pole refers to a nonimmunological mechanism evidenced by the presence of toxic metabolites or free radicals that lead to destruction of melanocytes (***Agrawal et al., 2004 and Pelle et al., 2005***).

One of the suggested nonimmunological mechanisms is apoptosis (programmed cell death), which is thought to cause reduction in the number of keratinocytes and their ability to produce adequate amounts of specific