

# BROADBAND UVA VERSUS PUVA IN THE TREATMENT OF EARLY STAGE MYCOSIS FUNGOIDES: A COMPARATIVE STUDY

## **Thesis**

**Submitted for the Fulfillment of the M.D. Degree in**

**Dermatology**

*By*

**Rehab Aly Abdel Salam Hegazy**

(M.B.B.Ch.; M.Sc.)

*Supervised By*

*Prof. Dr.* **Shahira Abdel Rahman Ramadan**

Professor of Dermatology  
Faculty of Medicine, Cairo University

*Dr.* **Safinaz Salah Eldin Sayed**

Associate Professor of Histology  
Faculty of Medicine, Cairo University

*Dr.* **Marwa Mohamed Fawzi**

Lecturer of Dermatology  
Faculty of Medicine, Cairo University

**Faculty of Medicine**

**Cairo University**

**2009**

بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

صدق الله العظيم

سورة البقرة الآية (٣٣)

# ABSTRACT

**Background:** Mycosis fungoides (MF) is the most common type of cutaneous-T-cell lymphoma, with no established consensus for its treatment. The standard treatment for early stage MF is PUVA. UVA1 phototherapy was found to induce marked improvement in skin lesions of patients with stages IA and IB MF. Broad band UVA is composed of 80.1% UVA1, with similar mechanisms of action.

**Aim of work:** The aim of the present work was to compare the efficacy of PUVA versus broad band UVA as a substitute to UVA1 in the treatment of early stage MF (IA, IB, IIA).

**Patients and methods;** Thirty patients with early stage MF (IA and IB) were included in this prospective, randomized clinical trial. They were randomly divided into two equal groups; group A [15 patients receiving PUVA] and group B [15 patients receiving BBUVA at 20J/cm<sup>2</sup>/ session]. The patients received 3 sessions/week for 13 weeks i.e. forty sessions. The patients were compared regarding clinical, histopathological, immunohistochemical (By measuring the bcl-2 level) and overall responses.

**Results:** Among each of the two groups, there was statistically significant improvement in the clinical, histopathological, immunohistochemical and overall responses. However there was no statistically significant difference between both groups in any of the aspects with comparable overall success rates; (93.3%) in the PUVA group and (80%) in the BBUVA group. Excellent overall response rates was higher in the BB-UVA group (41.7%) versus (14.3%) in the PUVA group, but still with no statistically significant difference (P=0.117).

As regards the side effects encountered in both groups; there was no statistically significant difference in the rates of tanning, pruritus, appearance of new lesions, photosensitivity or dryness. However discomfort was significantly higher among the BB-UVA group (P=0.032) and nausea was significantly higher among the PUVA group (P=0.003).

**Conclusion:** BB-UVA is a new, yet promising therapeutic modality in the treatment of early stage MF, as it is comparable to PUVA, as regards both the efficacy and safety. It could substitute the use of UVA1 in the treatment of early stage MF specially in pigmented skin (phototype  $\geq$  III) that can withstand longer periods of phototherapy without phototoxicity.

**Keywords:** *Mycosis fungoides, PUVA, Broad band-UVA, UVA1, phototherapy, Bcl-2.*

# ACKNOWLEDGMENT

*Praise be to ALLAH who exalted in knowledge whom he wills; but above those that have knowledge, there is one more knowing. The cherisher and sustainer of all what is in heavens and what is on earth; to Him is the goal and to Him is the return of all.*

*No words can describe my thanks and gratitude to Prof. Dr. Medhat El Mofty, who is responsible for the foundation of the phototherapy unit of our department and its computerized database for patients' filing system. His unlimited passion to science is always inspiring to us all and his endless giving is unparalleled.*

*I would like to express my deepest gratitude to Prof. Dr. Shahira Abdel Rahman Ramadan, Professor of Dermatology, Faculty of Medicine, Cairo University, for her continuous encouragement and correction. To me, she is so much more than a professor, she is an idol. She is truly an example to follow.*

*Endless thanks to Dr. Safinaz Salah Eldin Sayed, Assistant Professor of Histology, Faculty of Medicine, Cairo University for her constructive criticism,*

*invaluable advice and excellent supervision. Her time and supreme effort are clear in every part of this work.*

*I am deeply indebted to Dr. Marwa M. Fawzi, Lecturer of Dermatology, Faculty of Medicine, Cairo University. Her Critical insight and particular impetus given to this thesis will always be appreciated. Her never stopping help and advice, on every level, are corner stones of this work.*

*I am also grateful to Prof. Dr. Nermin El-Eishi, Assistant Professor of Dermatology, Faculty of Medicine, Cairo University for her valuable help.*

*I would like to thank all the staff members and colleagues at the department of Dermatology, for their sincerity, keenness and for setting an excellent example by just being who they are.*

*Rehab Hegazy  
2009*

# LIST OF ABBREVIATIONS

AIF	: Apoptosis inducing factor
AP-1	: Activator protein-1
APAF	: Apoptotic protease-activating factor
BB-UVA	: Broad band-ultraviolet A
BCNU	: Bischlorethyl nitrosuea
BH	: Bcl-2 homology
BSA	: Body surface area
CCL	: Chemokine ligands
CCR	: Chemokine receptors
CLA	: Cutaneous lymphocyte-associated antigen
CMV	: Cytomegalovirus
COX-2	: Cyclooxygenase-2
CT	: Computed tomography
CTCL	: Cutaneous T-cell lymphoma
DISC	: Death-inducing signaling complex
EBV	: Epstein-Barr virus
FADD	: Fas associated protein with death domain
FDA	: Food & drug administration
G-CSF	: Granulocyte colony stimulating factor
GM-CSF	: Granulocyte-macrophage colony stimulating factor
HD	: High dose
HIV	: Human immunodeficiency virus
HN-2	: Nitrogen mustard
HSV	: Herpes simplex virus
HTLV	: Human T-cell lymphotropic virus
ICAM-1	: Intercellular adhesion molecule-1

IL	: Interleukin
INF	: Interferon
LD	: Low dose
LN	: Lymph node
MD	: Moderate dose
MEL	: Monochromatic excimer light
MF	: Mycosis fungoides
MMP	: Matrix metalloproteinase
MOP	: Methoxypsoralen
mRNA	: Messenger RNA
MSH	: Melanocyte-stimulating hormone
NF-KB	: Nuclear factor-kappa Beta
PCR	: Polymerase chain reaction
PG	: Prostaglandin
PLE	: Polymorphous light eruption
PUVA	: Psoralen plus ultraviolet A
QOL	: Quality of life
RARs	: Retinoic acid receptors
RXRs	: Retinoid X receptors
sBCC	: Superficial basal cell carcinoma
SCC	: Squamous cell carcinoma
SMAD	: Transcription factor proteins
TBI	: Tumor burden index
TCR	: T-cell receptor
TCRGR	: T-cell receptor gene rearrangement
TGF	: Transforming growth factor
Th1	: T helper 1
Th2	: T helper 2

TLRs	: Toll-like receptors
TNF	: Tumor necrosis factor
TNF- $\alpha$	: Tumor necrosis factor-alpha
TNM	: Tumor-node-metastasis
TNMB	: Tumor-node-metastasis-blood
TSEB	: Total skin electron beam
UV	: Ultraviolet
UVA	: Ultraviolet-A
UVB	: Ultraviolet-B
$\alpha$ -MSH	: Alpha-melanocyte stimulating hormone



# LIST OF FIGURES

<b>Figure No.</b>	<b>Title</b>	<b>Page No.</b>
1.	Mycosis fungoides: A cancer of skin-homing T-cells ( <i>Giardi et al., 2004</i> )	5
2.	Roles for chemokine receptors in Mycosis fungoides ( <i>Hwang et al., 2008</i> )	6
3.	Patch-stage MF ( <i>Keehn et al., 2007</i> )	9
4.	Poikilodermatous variant of MF ( <i>Keehn et al., 2007</i> )	9
5.	Plaques of MF ( <i>Keehn et al., 2007</i> )	10
6.	Tumor stage MF ( <i>Keehn et al., 2007</i> )	10
7.	Histopathological diagnosis of MF ( <i>Hwang et al., 2008</i> )	13
8.	Spectra of ultraviolet light sources utilized in the treatment of CTCL ( <i>Baron and Stevens, 2003</i> )	41
9.	Molecular structure of commonly used psoralens ( <i>Honigsmann and Schwarz, 2008</i> )	44
10.	Schematic reproduction of biological effects of UVA-1 on skin diseases ( <i>Kroft et al., 2008</i> )	57
11.	Intrinsic and extrinsic pathways of apoptosis ( <i>Merino and Bouillet, 2009</i> )	68
12.	The Bcl-2 family members ( <i>Merino and Bouillet, 2009</i> )	69
13.	Sex distribution of patients receiving BB-UVA & PUVA	81
14.	Clinical & histopathological evaluation of PUVA patients at session 0	86
15.	Clinical & histopathological evaluation of PUVA patients at session 40	89
16.	Clinical, histopathological & immunohistochemical response of PUVA patients at session 40	89
17.	Comparing clinical, histopathological & immunohistochemical evaluation of sessions 0 & 40 among PUVA patients	90
18.	Overall evaluation of PUVA patients	90

<b>Figure No.</b>	<b>Title</b>	<b>Page No.</b>
19.	Clinical & histopathological evaluation of BB-UVA patients at session 0	<b>92</b>
20.	Clinical & histopathological evaluation of BB-UVA patients at session 40	<b>95</b>
21.	Clinical, histopathological and immunohistochemical response of BB-UVA patients at session 40	<b>95</b>
22.	Comparing clinical, histopathological, immunohistochemical evaluation at sessions 0 & 40 among BB-UVA patients	<b>96</b>
23.	Overall evaluation of BB-UVA patients	<b>96</b>
24.	Bcl-2 decrease correlated to the decrease of CD <sub>4</sub>	<b>101</b>
25.	Comparison of overall success rates between group A (PUVA) and group B (BB-UVA) patients	<b>102</b>
26.	Comparison of overall excellent responses between group A (PUVA) and group B (BB-UVA) patients	<b>103</b>
27.	Comparing total UV dose in groups A & B at session 40	<b>105</b>
28.	A female patient with MF plaques (stage IB) over the back (A) and after BB-UVA (B)	<b>106</b>
29.	The same patient with MF plaques over the chest (A) and after BB-UVA (B)	<b>106</b>
30.	A male patient with MF plaques (stage IB) before therapy (A) and after therapy with BB-UVA (B)	<b>107</b>
31.	A female patient with MF hypopigmented lesions before therapy (A) and after BB-UVA (B)	<b>107</b>
32.	A female patient with MF plaques (stage IB) over back (A) and after BB-UVA (B)	<b>108</b>
33.	The same patient with MF plaques over lower limbs (A) and after BB-UVA (B)	<b>108</b>
34.	A male patient with MF plaques (stage IB) over back (A) and after BB-UVA (B and C)	<b>109</b>
35.	The same patient with MF plaques over chest and abdomen (A) and after BB-UVA (B and C)	<b>109</b>

<b>Figure No.</b>	<b>Title</b>	<b>Page No.</b>
36.	A female patient with MF plaques before therapy (A) and after receiving 40 sessions of PUVA therapy (B)	<b>110</b>
37.	A male patient with MF plaques before therapy (A) and after receiving 40 PUVA sessions (B)	<b>110</b>
38.	A female patient with MF plaques over chest (A), back (B) and lower limbs (C)	<b>111</b>
39.	The same patient after receiving 40 sessions of PUVA therapy	<b>111</b>
40.	(A) A photomicrograph of a section in the skin of a patient with MF stage IB (H & E)	<b>112</b>
	(B) A photomicrograph of a section in the skin of the same patient after receiving 40 sessions of BB-UVA (H & E)	
41.	(A) A photomicrograph of a section in the skin of a patient with MF stage IB (H & E)	<b>113</b>
	(B) A photomicrograph of a section in the skin of the same patient after receiving 40 sessions of BB-UVA (H & E)	
42.	(A) A photomicrograph of a section in the skin of a patient with MF stage IB (H & E)	<b>114</b>
	(B) A photomicrograph of a section in the skin of the same patient after receiving 40 sessions of PUVA therapy (H & E)	
43.	(A) A photomicrograph of a section in the skin of a patient with MF stage IB (H & E)	<b>115</b>
	(B) A photomicrograph of a section in the skin of the same patient after receiving 40 sessions of PUVA therapy (H & E)	
44.	(A) A photomicrograph of a section in the skin of a patient with MF stage IB showing positive Bcl-2 immunostaining of the densely infiltrating cells in the papillary dermis	<b>116</b>
	(B) A photomicrograph of a section in the skin of the same patient after receiving 40 sessions of BB-UVA showing negative Bcl-2 immunostaining within the papillary dermis	

<i><b>Figure No.</b></i>	<i><b>Title</b></i>	<i><b>Page No.</b></i>
45.	(A) A photomicrograph of a section in the skin of a patient with MF stage IB showing positive Bcl-2 immunostaining of the densely infiltrating cells in the papillary dermis  (B) A photomicrograph of a section in the skin of the same patient after receiving 40 sessions of BB-UVA showing negative Bcl-2 immunostaining within the papillary dermis	<b>117</b>
46.	(A) A photomicrograph of a section in the skin of a patient with MF stage IB showing positive Bcl-2 immunostaining of the densely infiltrating cells in the papillary dermis  (B) A photomicrograph of a section in the skin of the same patient after receiving 40 sessions of PUVA showing negative Bcl-2 immunostaining within the papillary dermis	<b>118</b>
47.	(A) A photomicrograph of a section in the skin of a patient with MF stage IB showing positive Bcl-2 immunostaining of the densely infiltrating cells in the papillary dermis  (B) A photomicrograph of a section in the skin of the same patient after receiving 40 sessions of PUVA therapy, showing marked reduction in the mean area percent of Bcl-2 immunostaining	<b>119</b>

# LIST OF TABLES

<i>Table No.</i>	<i>Description</i>	<i>Page No.</i>
1.	TNMB staging system for MF	15
2.	TNM staging for MF	16
3.	Staging and treatment of mycosis fungoides or sezary syndrome	40
4.	PUVA responsive diseases	43
5.	Clinical items fulfilled for plaque type MF during follow up sessions	76
6.	Clinical items fulfilled for hypopigmented MF during follow up sessions	77
7.	Histopathological items fulfilled during follow up sessions	78
8.	Data of patients included in the PUVA group (group A)	82
9.	Data of patients included in the BB-UVA group (group B)	83
10.	Stages of MF included in the study	84
11.	Clinical success rates among PUVA and BB-UVA patients	97
12.	Clinical excellent response among PUVA and BB-UVA patients	98
13.	Histopathological success rates among PUVA and BB-UVA patients	98
14.	Histopathological excellent responses among PUVA and BB-UVA patients	99
15.	Immunohistochemical success rates among PUVA and BB-UVA patients	99
16.	Immunohistochemical excellent responses among PUVA and BB-UVA patients	100
17.	Overall success rates among PUVA and BB-UVA patients	102
18.	Overall excellent responses among PUVA and BB-UVA patients	103
19.	Side effects in both groups	104

# CONTENTS

	<i>Page</i>
<b>AKNOWLEDGEMENT .....</b>	<b>i</b>
<b>LIST OF ABBREVIATIONS .....</b>	<b>iii</b>
<b>LIST OF FIGURES .....</b>	<b>vi</b>
<b>LIST OF TABLES .....</b>	<b>x</b>
<b>INTRODUCTION AND AIM OF WORK .....</b>	<b>I</b>
<b>REVIEW OF LITERATURE:</b>	
▪ Mycosis Fungoides .....	<b>1</b>
▪ Psoralen Plus Ultraviolet A (PUVA) .....	<b>41</b>
▪ Broad Band UVA and Ultraviolet A1 (UVA1) .....	<b>56</b>
▪ Bcl-2 .....	<b>67</b>
<b>PATIENTS AND METHODS .....</b>	<b>72</b>
<b>RESULTS .....</b>	<b>81</b>
<b>CASE PRESENTATIONS .....</b>	<b>106</b>
<b>DISCUSSION .....</b>	<b>120</b>
<b>SUMMARY .....</b>	<b>131</b>
<b>REFERENCES .....</b>	<b>135</b>
<b>ARABIC SUMMARY .....</b>	

## INTRODUCTION

Mycosis Fungoides (MF), a low grade lymphoproliferative disorder, is the most common type of cutaneous T-cell lymphoma. Typically, neoplastic T-cells localize to the skin and produce patches, plaques, tumors or erythroderma. Diagnosis of MF can be difficult due to highly variable presentations and sometimes non specific nature of histological findings (*Nashan et al., 2007*).

Several reviews and guidelines on the management of MF have been published; however, treatment strategies for patients with MF vary from institution to institution and no consensus has yet been agreed upon (*Trautinger et al., 2006*).

Treatment of MF is indicated to reduce symptoms, improve clinical appearance, prevent secondary complications, and prevent progression of disease, all of which may have an impact on survival. Treatment of MF includes topical and systemic therapies, which can be administered alone or in combination (*Lundin and Osterborg, 2004*).

MF is one of the major dermatologic conditions for which phototherapy continues to be a valuable treatment modality (*Baron and Stevens, 2003*).

The standard treatment for early stage MF is photochemotherapy with methoxsalen plus UVA (320 to 400 nm) exposures (PUVA therapy) (*Zane et al., 2001*). Irradiation devices that allow treatment of patients' skin with selected emission spectra are increasingly being used, as high dose UVA1 therapy (which selectively employs long wave UVA