A Comparative Study of the Effect of Narrow Band Ultraviolet –B (NB-UVB) Phototherapy and Ultraviolet –A with Psoralen (PUVA) Photochemotherapy on Serum Levels of Soluble Interleukin -2 Receptor (SIL-2R) before and after Treatment in Psoriatic Patients

Thesis

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By

Marwa Gomaa Mohamed El-Feky
(M.B., B.Ch)
Ain Shams University

Under the supervision of

Prof. Dr. Nagwa Mohamed Youssef
Professor and Head of the Department of Dermatology and Venereology Faculty of Medicine
Ain Shams University

Dr. Marwa Salah El-Din Zaki
Lecturer of Dermatology and Venereology
Faculty of Medicine
Ain Shams University

Dr. Hanaa Mohamed El-Sayed Emam
Assistant professor and Head of Dermatology and Venereology
Research Department –National Research Center

Faculty of Medicine
Ain Shams University
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List of Contents

Title	Page
CHAPTER I: INTRODUCTION AND AIM OF THE WORK	1
CHAPTER II: REVIEW OF LITERATURE	6
Section I: An overview of psoriasis	6
I.A. Epidemiology	6
I.B. Clinical picture of psoriasis	7
I.C. Aetiopathogenesis of psoriasis	14
I.C.1. Genetic predisposition	15
I.C.2. Precipitating factors	16
I.C.3. Immunopathogenesis of psoriasis	23
I.D. Histopathology of psoriasis	32
I.E. Treatment of psoriasis	35
I.E.1. Topical Therapies	35
I.E.2. Phototherapy	37
I.E.3. Systemic Therapy	38
I.E.4. Biological Therapy	39
I.E.5. Combination, Rotational and Sequential Treatment	43
Section II: Phototherapy in psoriasis	46
II.A. Ultraviolet Radiation	46
II.B. Psoralen Photochemotherapy (PUVA) in psoriasis	48
II.B.1. Historic Aspects	49
II.B.2. Psoralens	49
II.B.3. Mechanism of action of PUVA.	50
II.B.4. Indications of PUVA in Psoriasis	53
II.B.5. Side effects of PUVA	54
II.B.6. PUVA Monitoring Guidelines	58
II.B.7. Contraindications to PUVA Therapy	59
II.B.8. UVA dosimetry and individual sensitivity	61
II.B.9. PUVA protocols for treatment of psoriasis	62
II.C. Narrow-Band (NB) UVB Phototherapy in Psoriasis	63
II.C.1. Historic Aspects	63
II.C.2. Advantages of NB-UVB	64
II.C.3. NB-UVB protocols for treatment of psoriasis	65
II.C.4. Mechanism of action of NB-UVB in psoriasis	67
II.C.5. Narrow-band UVB phototherapy combination	69
II.C.6. Contraindications	69
II.C.7. Adverse effects of NB-UVB	69

List of Contents (Cont.)

Title	Page

Section III: Interleukin-2 and Interleukin-2 Receptor 72
III.A. General features of cytokines 72
III.B. Interleukin-2 74
III.B.1. Historical Background 74
III.B.2 Genetics 74
III.B.3. Biochemistry 75
III.B.4. Sources 75
III.B.5. Actions of IL-2 75
III.B.6. Diseases associated with IL-2 79
III.C. Interleukin-2 Receptors 80
III.C.1. Historical Background 80
III.C.2. Biochemical Structure 81
a. Alpha (α) subunit of IL-2R 82
b. Beta (β) chain of IL-2R 82
c. Gamma (γ) chain of IL-2R 82
III.C.3. Sources of IL-2R 84
III.C.4. Regulation of IL-2R Expression 84
III.C.5. Actions 85
III.C.6. The IL-2 receptor as a target for immunotherapy 87
III.D. Methods of Assay of sIL-2R 88
III.D.1. Radioimmunoassay (RIA) 88
III.D.2. Enzyme linked immunosorbent assay (ELISA) 89

CHAPTER III: SUBJECTS AND METHODS 91

CHAPTER IV: RESULTS 103

CHAPTER V: DISCUSSION 114

CHAPTER VI: SUMMARY AND CONCLUSION 122

CHAPTER VII: REFERENCES 126

ARABIC SUMMARY ..... --

List of Tables

Tab. No	Subjects	Page
1.	A quality of life-based definition of mild, moderate and severe psoriasis	8
2.	Potential psoriasis-susceptibility loci	16
3.	Cytokines and chemokines that play a role in the immunologic cascade of psoriasis	32
4.	The mechanism of action, dosage as well as common side effects of topical therapies used	36
5,6,7.	Systemic drugs in psoriasis (methotrexate, cyclosporine and oral retinoids)	38
8.	Targeted biologic strategies for the treatment of psoriasis	41
9.	The side effects, dosage and monitoring required for the biologics	42
10.	Systemic sequential therapy with cyclosporine and acitretin	45
11.	The difference between UVA and UVB	48
12.	PUVA monitoring guidelines	59
13.	Contraindications to PUVA therapy	60
14.	Scale for grading erythema	61
15.	Skin phototypes	61
16.	Summary of the data of the patients and control groups	104
17.	Comparison within group 1 (G1) before and after treatment as regards the mean PASI score and sIL-2R level	106
18.	Comparison within group 2 (G2) before and after treatment as regards the mean PASI score and sIL-2R level	107

List of Tables (Cont.)

Tab. No	Subjects	Page
19.	Comparison between group 1 (G1) and group 2 (G2) after treatment as regards the mean PASI score	109
20.	Comparison between group 1 (G1) and group 2 (G2) after treatment as regards the mean sIL-2R level	110
21.	Correlation coefficient between sIL-2R and PASI within group 1 (G1) and group 2 (G2) before treatment	111
22.	Correlation coefficient between sIL-2R and PASI within group 1 (G1) and group 2 (G2) after treatment	113

List of Figures

Fig. No	Subjects	Page
1.	T-lymphocyte activation by APCs	27
2.	T cell binding and trafficking into the dermis and epidermis	30
3.	The psoriatic cascade	31
4.	Histology of psoriasis	34
5.	Immunobiologics that target APC-T cell interaction	40
6.	Algorithm for the treatment of plaque psoriasis in healthy adults	45
7.	Classification of UV and visible radiation according to wavelength	47
8.	Chemical structure of 8-methoxypsoralen, trimethylpsoralen and 5-methoxypsoralen	50
9.	IL-2 is generated by Th cells	78
10.	The structure of high affinity IL-2R	81
11.	Comparison among the controls and the two groups of patients before treatment as regards the mean SIL-2R level	105
12.	Comparison within group 1 (G1) before and after treatment as regards the mean PASI score	106
13.	Comparison within group 1 (G1) before and after treatment as regards the mean sIL-2R level	107
14.	Comparison within group 2 (G2) before and after treatment as regards the mean PASI score	108
15.	Comparison within group 2 (G2) before and after treatment as regards the mean sIL-2R level	108

List of Figures (Cont.)

Fig. No	Subjects	Page

16. Comparison within group 2 (G2) before and after treatment as regards the mean sIL-2R level 109

17. Comparison between group 1 (G1) and group 2 (G2) after treatment as regards the mean sIL-2R level 110

18. Correlation coefficient between sIL-2R and PASI within group 1 (G1) and group 2 (G2) before treatment 112

19. Correlation coefficient between sIL-2R and PASI within group 1 (G1) and group 2 (G2) after treatment 113

List of Abbeviations

AA.....Arachidonic acid
ADCC.....antibody-directed cellular cytolysis
AIDS.....Acquired immune deficiency syndrome
ANOVA.....One way analysis of variance
APC.....Antigen presenting cell
ATL.....Adult T- cell leukaemia
BB-UVB.....Broad band- ultraviolet B
BSA.....Body surface area
cAMP.....Cyclic adenosine monophosphate
CD.....Cluster of differentiation
cDNA.....Cyclic deoxy ribonucleic acid
CLA.....Cutaneous lymphocyte antigen
cm.....centimeter
CsA.....Cyclosporine
CTL.....Cytotoxic T- lymphocyte
CTLA.....Cytotoxic T-lymphocyte-associated antigen
DNA.....Deoxy ribonucleic acid
EGF.....Epidermal growth factor
ELISA.....Enzyme linked immunosorbent assay
FDA.....Food and Drug Adminstration
g.....gram
G.....Group
GM-CSF.....Granulocyte macrophage colony stimulating factor
HIV.....Human immunodeficiency virus
HLA.....Human leukocyte antigen
HSV.....Herpes simplex virus
HTLV-1.....Human T-lymphotrophic retrovirus type-1
ICAM.....Intercellular adhesion molecule
IFN-γ.....Interferon gamma
IL-2.....Interleukin-2
IL-2Rα.....Interleukin-2 receptor alpha
ILF.....Interleukin-enhancer binding factor
IM.....Intramuscular
IP.....Inducible protein
IV.....Intravenous
J/cm2.....Joules per square centimeter of irradiated skin

List of Abbeviations (Cont.)

Kb ..... Kilo base
kD ..... Kilodaltons
Kg ..... Kilogram
L ..... Liter
LAK ..... Lymphokine activated killer cells
LC ..... Langerhans cell
LFA ..... Leucocyte function associated antigen
MED ..... Minimal erythema dose
mg ..... milligram
MHC ..... Major histocomptability complex
MIG ..... Monokine induced by interferon gamma
mj/cm^2 ..... milli joules per square centimeter of irradiated skin
ml ..... Milli
mm ..... millimeter
5-MOP 5-methoxypsoralen
8-MOP 8-methoxypsoralen
MPD ..... Minimal phototoxic dose
mRNA ..... Messenger ribonucleic acid
mW/cm^2 ..... milliwatt per square centimeter of irradiated skin
MXT ..... Methotrexate
NB-UVB ..... Narrow-band ultraviolet-B
NGF ..... Nerve growth factor
NK ..... Natural killer
nm ..... nanometer
NPF ..... National Psoriasis Foundation
P ..... Psoralen
PASI ..... Psoriasis area and severity index
PG ..... Prostaglandin
pg ..... picogram
PLE ..... Polymorphic light eruption
PMNL ..... Polymorphonuclear leucocytes
PPD ..... Purified protein derivative
PSORS ..... Psoriasis susceptibility locus
PUFA ..... Polyunsaturated fatty acid
PUVA ..... Psoralen and ultraviolet A
QOL ..... Quality of life

List of Abbeviations (Cont.)

r.....Pearson correlation coefficient
RA.....Rheumatoid arthritis
RCT.....Randomized controlled trials
RF.....Rheumatoid factor
RIA.....Radioimmunoassay
RNA.....Ribonucleic acid
SC.....Subcutaneous
SD.....Standard deviation
SDS-PAGE.....Sodium dodecyl sulphate polyacrylamide gel electrophoresis
SIL-2Rα.....Soluble interleukin-2 receptor alpha
SLE.....Systemic lupus erythematosus
SP.....Substance P
SPSS.....Statistical package for social science
TB.....Tuberculosis
Tc.....Cytotoxic T cell
TCGF.....T-cell growth factor
TCR.....T cell receptor
TGF.....Transforming growth factor
Th.....Helper T cell
TIL.....Tumor infiltrating lymphocytes
TMP.....4,5,8-trimethyl psoralen
TNF-α.....Tumor necrosis factor alpha
tx.....therapy
UCA.....Urocanic acid
URI.....Upper respiratory infection
UV.....Ultraviolet
UVA.....Ultraviolet A
UVB.....Ultraviolet B
UVC.....Ultraviolet C
UVR.....Ultraviolet radiation
VCAM.....Vascular cell adhesion molecule
VDR.....Vitamin D receptor
VEG-F.....Vascular endothelial growth factor
VLA.....Very late appearing antigen

CHAPTER I

INTRODUCTION & AIM OF THE WORK

Introduction:

Psoriasis is a common chronic condition characterized by thick scaling red plaques which can be either localized or widespread ***(Gelfand et al., 2005)***. The characteristic histological finding of psoriasis is epidermal hyperproliferation with focal accumulation of neutrophils and lymphocytes. Above these foci, the granular layer is absent with parakeratosis, the accumulation of neutrophils within a spongiotic pustule is referred to as a "spongiform pustule of Kogoj" and the accumulation of neutrophil remnants in the stratum corneum, as a "microabscess of Munro"**.** In the dermis the capillaries are dilated and tortuous with marked edema especially at the tops of the papillae. There is a mixed perivascular infiltrate of lymphocytes, macrophages and neutrophils ***(Ozawa and Aiba, 2004)***.

Psoriasis is considered to be a genetically programmed disease of dysregulated inflammation, which is driven and maintained by multiple components of the immune system. The pathologic collaboration between innate immunity (mediated by antigen presenting cells and natural killer T-lymphocytes) and acquired immunity (mediated by T-lymphocytes) results in the production of cytokines, chemokines and growth factors that contribute to the inflammatory infiltrate seen in psoriatic plaques ***(Gaspari, 2006)***.

Although the exact etiopathogenesis is unknown, there is growing evidence that activated T cells are the primary modulators in the pathogenesis of psoriasis causing keratinocyte hyperproliferation in the epidermis. This is further supported by the fact that increased levels of activated T lymphocytes are present in psoriatic skin plaques and blood of patients ***(Ellis and Krueger, 2001).*** The majority of T lymphocytes that localize to the dermis are of the CD4+ helper type, while those that migrate to the epidermis are predominantly of CD8+ cytotoxic type ***(Menssen et al., 1995).***

The activation of T cells by antigen-presenting cells (APCs) involves a cascade of pathways that ultimately leads to the production of a variety of cytokines which subsequently stimulate further T-cell activation, proliferation and cytokine production. The type 1/type 2 (Th1/Th2) paradigm describes two major classes of T cells that can be differentiated according to their cytokine patterns. T cells that produce IL-2, interferon (IFN)-γ and TNF-α are termed Th1 cells and contribute to cell-mediated immunity. Conversely, T cells that release IL-4, IL-5 and IL-10 are termed Th2 cells, which augment humoral responses. Th1 cytokines are proinflammatory and Th2 cytokines are anti-inflammatory ***(Szabo et al., 1998).*** Psoriasis can be considered as a Th1 dominant disease and as such produces a cytokine response with potent antibacterial properties ***(Prinz, 2001)***.

The involvement of T-lymphocytes in the pathogenesis of psoriasis can be described in terms of 4 events: the initial activation of T-lymphocytes, the proliferation and

differentiation of T- cells, the trafficking of T cells, and lastly the reactivation of T-cells ***(Michael and Alan, 2006*).**

Interleukin -2 (IL-2) is a lymphokine synthesized and secreted primarily by T helper lymphocyte. IL-2 stimulates the production of IL-2 receptor α (IL-2Rα) on the T cell surfaces. IL-2Rα is then released to the serum as a measurable protein; soluble interleukin -2 receptor (SIL-2R). The amount of sIL-2R is proportionally related to the amount of IL-2Rα expressed on the T cell surface ***(Goldsmith and Greene, 1994).*** Many studies have shown that serum sIL-2R levels are raised in patients with chronic plaque psoriasis ***(De Rie et al., 1996).*** Other studies have indicated that sIL-2R levels are well correlated with psoriasis area and severity index (PASI) score before and after treatment. Therefore, plasma sIL-2R levels could be regarded as a marker in psoriasis vulgaris activity during treatment ***(Zalewska et al., 2006).***

Phototherapy has been known as an effective agent for the treatment of moderate to severe psoriasis, and it may be used in treatment of mild form of psoriasis in case of failure of topical therapy or if the site of psoriasis is psychologically devastating as facial psoriasis, scalp psoriasis or psoriasis of the palms ***(Lebwohl, 2005)***.

The efficacy of narrow-band ultraviolet-B (NB-UVB) for the treatment of psoriasis has been attributed to interference with DNA, RNA and protein synthesis in the hyperproliferative psoriatic plaques, alteration of various cytokines and other mediators of inflammation, as well as immunological effects**.** UVB also induces the expression of the tumour suppressor gene

P53, and this can lead to either cell cycle arrest or apoptosis of keratinocytes ***(Paul et al., 1994; Ibbotson et al., 2004). Sigmundsdottir et al. (2005)*** have demonstrated that the combination of UVB-induced apoptosis, increased secretion of anti-inflammatory cytokines and decreased trafficking to the skin may help to explain the beneficial effects of UVB treatment on psoriasis. However, ***De Rie et al. (1998)*** found that sIL-2R serum levels were not decreased in psoriatic patients receiving NB-UVB in spite of clinical improvement indicating that treatment does not induce systemic immunosuppression. It is therefore clear that the detailed mechanisms of action of TL-01 are not well defined (***Ibbotson et al., 2004).***

On the other hand, psoralen plus ultraviolet radiation (PUVA) is well documented to reduce circulating T lymphocyte numbers and function leading to return of circulating helper / induced T cell numbers to normal with long term therapy by inducing apoptosis in lymphocytes. The conjunction of psoralens with epidermal DNA inhibits DNA replication and causes cell cycle arrest. Psoralen photosensitivity also causes an alteration in the expression of cytokines and cytokine receptors ***(Honigsmann, 2001). Duncan et al. (1991)*** studied the effect of PUVA therapy on sIL-2R serum levels in psoriatic patients. It was found that levels of sIL-2R showed a strong correlation with PASI and found that PUVA significantly reduced the PASI and sIL-2R levels to a similar degree after 4 weeks of treatment.

Aim of the Work:

The aim of this work is to compare the effect of NB-UVB phototherapy and PUVA photochemotherapy on sIL-2R serum level as a marker of systemic T-cell activation in patients with psoriasis before and after treatment. A correlation will also be done between the severity of psoriasis as expressed by the PASI score and sIL-2R serum levels.