BILATERAL COMPARATIVE STUDY OF THE EFFECT OF SUBERYTHEMOGENIC DOSES OF NB-UVB VERSUS ERYTHEMOGENIC DOSES IN TREATMENT OF CHRONIC PLAQUE PSORIASIS

Thesis

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Abstract

Background: Psoriasis is a major common and relapsing disease which is both physically and psychologically disabling.

Narrow band UVB (NB-UVB) is a new phototherapy option for psoriasis due to its easy administration and less acute and remote hazards than other forms of phototherapy.

Aim: In this study, a double half bilateral comparative trial on 20 patients with chronic plaque psoriasis was carried out to compare suberythemogenic dose of NB-UVB versus erythemogenic dose in the treatment of psoriasis.

Patient and method: Our study was conducted on 20 patients with chronic plaque psoriasis. Half body UV exposure was achieved by covering half of the body with an opaque overall cut in half length ways.
The left body side was treated with the dose causing minimal erythema (100% of MED) while the right side was given 70% of this minimal erythema dose (suberythemogenic side).

Results: Our results revealed no statistically significant difference in PASI final and in the percentage of reduction of PASI score between both sides as well as the total number of sessions (P-value > 0.05) while our most significant difference was the lower total cumulative UVB dose on the suberythemogenic side (P-value < 0.001).

Conclusion: Our study recommends reducing the dose regimen of NB-UVB and consequently the cumulative UVB dose by using the suberythemogenic dosing schedule as it does not only affect the therapeutic potential of NB-UVB, but also improves the benefit/risk ratio of NB-UVB therapy.

Key words: NB-UVB- Psoriasis- Suberythemogenic dose- Minimal erythemogenic dose

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List of Abbreviations

APC	Antigen presenting cells
BB-UVB	Broad band ultraviolet radiation type B
CD	Cluster of differentiation
CLA	Cutaneous lymphocyte associated antigen
CPD	Cyclobutane pyrimidine dimers
CRABP	Cellular retinoic acid binding protein
C-T	Cytosine-thymidine
DNA	Deoxyribo nucleic acid
GVHD	Graft versus host disease
HGPRT	Hypoxanthine guanine phosphoribosyl transferase
HLA	Human leukocyte antigen
ICAM-1	Inter-cellular adhesion molecule
IFN-γ	Interferon gamma
IgG	Immunoglobulin G
IL	Interleukin
LCs	Langerhans cells
LFA	Leukocyte function associated antigen
MCP	Monocyte chemoattractant protein
MED	Minimal erythema dose
MF	Mycoses fungoides
MHC	Major histocomptability complex
MMPs	Matrix metalloproteinases
MN	Micronucleus
MOP	Methoxy psoralen

MPD	Minimal phototoxic dose
MSH	Melanocyte stimulating hormone
NB-UVB	Narrow band ultraviolet radiation type B
NER	Nuclear excision repair
NFAT	Nuclear factor of activated T-cells
PASI	Psoriasis area and severity index
PBMCs	Peripheral blood mononuclear cells
PGE_2	Prostaglandin E_2
PLC	Pityriasis lichenoides chronica
PRP	Pityriasis rubra pilaris
PRR	Pathogen recognition receptors
PUVA	Psoralen + ultraviolet radiation type A
RAR β & γ	Retinoic acid receptors beta & gamma
SD	Standard deviation
TGF-α	Transforming growth factor-α
Th1 & Th2	T helper one & T helper two
TNF-α	Tumor necrosis factor-α
UVA, UVB&UVC	Ultraviolet radiation type A, ultraviolet radiation type B & ultraviolet radiation type C

Introduction

Psoriasis is a distressing, chronic disease that affects the skin. The disease varies in severity depending on inheritance and environmental factors; some patients have mild disease with isolated scaly erythematous plaques on the elbows, knees, or scalp, whereas others can have up to 100% of their cutaneous surface affected. It clearly has a potentially devastating effect on the patient's quality of life**.** The most common form of psoriasis is plaque psoriasis. Although psoriasis is characterized by proliferation of the epidermis, the immune system has a prominent role in development of this disease ***(Lebwohl et al., 2003).***

These data have aroused an increased awareness and interest in more aggressive management of psoriasis, coupled with a better understanding of immunopathogenesis; this has led to the development of new agents targeting specific cells and molecules involved in the development and maintenance of psoriatic plaques. Although many therapies including methotrexate, cyclosporin and PUVA showed significant efficacy, their side effect profiles have excluded their long term use ***(Winterfield et al., 2005).***

Narrow band UVB phototherapy is an effective treatment for psoriasis. Owing to its limited penetration, the direct effects of UVB are mostly restricted to cells residing the epidermis and papillary dermis, and are associated with epidermal depletion of Langerhans cells and T cells ***(Sigmundsdottir et al., 2005).***

Monochromatic 311-nm UVB produced clearing of plaque type psoriasis lesion at the smallest fraction of a MED dose compared with other wavelengths studied. Accordingly the idea that burning wavelengths could be separated from therapeutic wavelengths in the UVB spectrum was a result of many studies ***(Hofer et al., 1998 and Walters et al., 1999).***

It has been made clear that to reduce the side effects of any phototherapy, it is always necessary to investigate different dose regimens to find the regimen with the highest efficacy and the smallest cumulative dose ***(Hofer et al., 1998).***

Aim of Work

The aim of our work was to compare the efficacy of suberythemogenic dose of NB-UVB versus erythemogenic dose of NB-UVB in the treatment of chronic plaque psoriasis.

Our study was carried out to determine whether lessening the acute and remote side effects of NB-UVB by reducing the treatment cumulative UVB dose would affect the therapeutic response in patients with chronic plaque psoriasis.

Psoriasis

Psoriasis is a chronic disfiguring inflammatory condition of the skin in which both genetic and environmental influences have a critical role ***(Nevitt and Hutchinson, 1996).***

Aetiology and pathogenesis:

Although psoriasis is a disease of unsettled aetiology and pathogenesis, yet many factors are involved including:

- Epidermal proliferation as a result of an increase in the proliferating cell compartment (seven folds) in basal, suprabasal levels or the epidermis as a whole and not because of shortened cell cycle time ***(van de Kerkhof, 1999).***
- Angiogenic activity of epidermal keratinocytes which produce an array of soluble mediators including interleukin-8 (IL-8), transforming growth factor-α (TGF-α) and tumor necrosis factor (TNF-α) ***(Detmar et al., 1994).***
- Immunological involvement of T-lymphocytes in the development of psoriatic plaques proved by early influx of T-cells into lesions, increased antigen presentation in psoriatic plaques, strong association with major histocomptability complex (MHC), particularly human leukocyte antigen (HLA) Cw6 ***(Badsagard et al., 1989),*** and ablative effect of immunosuppressant and T-cell depleting agents ***(Olsen, 2001).***

T-cells and dendritic cells expressing auto- antigens which populate the normal skin of patients with psoriasis. These cells do not cause inflammation in their resting state but when stimulated by injury or

infection with organisms that trigger dendritic cell pathogen-recognition receptors (PRR) and activation of plasmacytoid predendritic cells ***(Nestle, 2005).*** Activated dermal dendritic cells in turn sparks the activation of auto- reactive T-cells leading to their proliferation within the dermis and T helper1 cells (Th1) and T helper2 (Th2) cells within epidermis. T helper2 cells secrete IL-10 which inhibits Th1 cytokines. Activated dendritic cells and auto reactive Th1 cells secrete inflammatory cytokines as interferon gamma (IFN-γ) and IL-2 that induce the production of monocyte chemo- attractant protein 1 (MCP-1). Those inflammatory cytokines cause recruitment of monocytes and macrophages. Also, other chemotactic factors secreted by keratinocytes, as IL-8, leads to influx of macrophages and dendritic cells that produce TNF-α. Tumor necrosis factor α (TNFα) drives the development of skin changes characteristic of psoriasiform dermatitis ***(Stratis, 2006).***

Histopathology of psoriasis:

The histopathology of psoriasis is characterized by regular epidermal hyperplasia with long, test tube shaped rete ridges, together with thinning over the dermal papillae, thus explaining Auspitz's sign. The granular layer is thin or absent, and there is overlaying parakeratosis. Small collections of neutrophils (Munro micrabscesses) may be present in the stratum corneum. The dermal papillae are prominent and contain ectatic vessels. There is a perivascular mononuclear cell infiltrate. In guttate lesions the epidermal hyperplasia may be less marked ***(Ragaz and Ackermann, 1979).***

Psoriasis may be distinguished from dermatitis by the paucity of edema, the absence of spongiosis and vesicle formation, the clubbing of the papillary bodies, and the tortuosity of the capillary loops ***(Ragaz and Ackermann, 1979).***

Clinical picture:

1. Psoriasis vulgaris:

This is the commonest pattern of psoriasis with circular plaques predominating mainly on the elbows, knees, lower back, the retroauricular areas of the scalp and the umbilicus. Single small lesions may become confluent, forming plaques, where the borders resemble a land map (geographic psoriasis). Lesions may extend laterally and become circinate because of the confluence of several plaques (Psoriasis gyrata). Occasionally there is partial central clearing, resulting in ring like lesions (annular psoriasis). Psoriasis vulgaris may be localized in the major skin folds such as the axillae, the genitocrural region, and the neck (psoriasis inverse), here scaling is absent and the lesions take the form of glossy, sharply demarcated erythema ***(Christophers and Mrowietz, 1999).***

2. Guttate (eruptive) psoriasis:

Typically this pattern presents as small (0.5-1.5 cm in diameter) lesions over the upper trunk and proximal extremities. Streptoccocal throat infection frequently precedes the onset or flare of guttate psoriasis ***(Camp, 1998)***.

3. Erythrodermic psoriasis:

Two forms of erythrodermic psoriasis exist; the first form is a gradual evolution of chronic plaque psoriasis into an exfoliative phase, and can be regarded as extensive plaques psoriasis involving all or almost

all the cutaneous surface. There are usually some areas of normal skin, the psoriatic characteristics are retained and the prognosis is good**.** The other form is part of unstable psoriasis. It may occur at any time, either presenting suddenly and unexpectedly or it is preceded by a period of increasing intolerance to local treatment or UV therapy or may follow generalized pustular psoriasis. The characteristics of the disease are lost and the patient may be febrile and ill ***(Camp, 1998).***

4. Pustular forms of psoriasis:

Pustular forms of psoriasis are classified into two main groups; localized and generalized forms. The localized forms are usually confined to the hands and feet and tend to be chronic. In the generalized forms, the whole body may be involved and the course may be subacute, acute or even fulminating and life threatening ***(Camp, 1998).***

The localized forms include palmoplantar pustulosis and acrodermatitis continua. Palmoplantar pustulosis is characterized by erythematous scaly plaques studded with sterile pustules. It affects mainly adults ***(Reitamo et al., 1992).***

On the other hand, acrodermatitis continua affects mainly children and is rare in young adults. It presents as a chronic, sterile, pustular eruption affecting initially the tips of fingers or toes which tends slowly to extend locally and may evolve in adults into generalized pustular psoriasis. It may be associated with osteolysis of the tuft of the distal phalynx ***(Mahowald and Parrish, 1982).***

The acute form of generalized pustular psoriasis (zumbusch) starts by high fever and severe malaise. The pre-existing psoriatic lesions become fiery red and develop pinpoint pustules. Sheets of erythema and

pustulation spread to involve previously unaffected skin and the flexures are mainly involved. Isolated pustules, lakes of pus, circinate lesions, plaques of erythema with pustular collarets may occur. Waves of pustulation may succeed each other, subsiding into exfoliation of the dried pustules. Nail and tongue affection are usually seen ***(Baker, 1984).***