COMPARISON STUDY OF NB-UVB ALONE Vs COMBINATION OF TOPICAL AGENTS WITH NB-UVB IN THE TREATMENT OF PSORIASIS

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CERTIFICATE

Certified that this dissertation entitled ***"COMPARISON STUDY OF NB-UVB ALONE Vs COMBINATION OF TOPICAL AGENTS WITH NB-UVB IN THE TREATMENT OF PSORIASIS"*** is a bonafide work done by **Dr. R.SOWMIYA,** Post Graduate Student of the department of Dermatology, Venereology and Leprosy, Madras Medical College, Chennai – 600 003, during the academic year 2007 – 2010. This work has not previously formed the basis for the award of any degree.

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CONTENTS

INTRODUCTION

Psoriasis is a common, genetically determined, inflammatory and proliferative disease of the skin, the most characteristic lesions consisting of chronic, sharply demarcated, dull red, scaly plaques, particularly on the extensor prominences and in the scalp.

The earliest description of what appears to represent psoriasis are given at the beginning of medicine in the Corpus Hippocraticum. Hippocrates used the terms psora and lepra for the conditions that can be recognized as psoriasis. Willan separated two diseases as psoriasis entities, a discoid lepra graecorum and a polycyclic confluent psora leprosa, which later was called psoriasis. Von Hebra definitely distinguished the clinical picture of psoriasis from that of Hansen's disease.

Psoriasis continues to be a therapeutic challenge in spite of our growing knowledge of its pathogenesis. Various forms of treatment have been developed in the past several decades and new regimens are constantly being tried. Narrowband ultraviolet-B phototherapy has become an increasingly popular modality in the treatment of psoriasis. Many studies have documented improved efficacy and therapeutic index for narrow band UVB in comparison with conventional broad band UVB irradiation. However the long term side effects of narrowband UVB therapy have not been fully documented. As a result, there has been a great deal of interest in

photocombination therapies that are capable of both reducing the cumulative UVB doses and accelerating resolution of skin lesions. Phototherapy can be combined with topical or systemic agents. Topical agents include anthralin, vitamin D analogues, retinoids, glucocorticoids, emollients, salt water baths and tar.

This study was designed to study the efficacy and safety of narrowband UVB and to study the advantages and disadvantages of photocombination with a topical steroid and topical tazarotene. `

REVIEW OF LITERATURE

NARROWBAND UVB PHOTOTHERAPY

HISTORY[1]

The ancient egyptians were the first to recognize the beneficial effect of sunlight. Newton in 1672 discovered the spectrum of visible light. Ultraviolet light was discovered in the early 1700s. In 1895, modern phototherapy began when Niels Finsen, the father of modern phototherapy, used a carbon arc source to treat lupus vulgaris. He was awarded the Nobel prize in 1903. In 1923, Dr.Wiliam Goeckerman treated psoriasis with UVB and crude coal tar. In 1953, Ingram introduced his regime combining artificial broadband UVB and dithranol. In 1978, Wiskemann introduced irradiation cabin with broad band UVB tubes for the treatment of psoriasis and uremic pruritus[2]. However the potential carcinogenic effect of broad band UVB made it less popular. Parish and Jaenicke[3] defined the action spectrum for psoriasis with a peak at 313nm. The breakthrough came after 1988, when narrow band UVB phototherapy was introduced for the treatment of psoriasis by Van Weelden et al and Green et al[4]. Since then,it has proven to be more effective in various skin disorders and is increasingly used in various parts of the world.

ELECTROMAGNETIC SPECTRUM[5,6]

Sunlight comprise a spectrum of electromagnetic waves from the very short cosmic rays, X-rays and gamma rays through ultraviolet light, visible light and infrared radiation to the long radio and television waves. Ultra violet radiation is a small component of the electromagnetic spectrum having a wavelength between 100 and 400nm. It is further subdivided into

1. UVC: 100 to 280nm
2. UVB: 280 to 315nm
3. UVA: 315 to 400nm

SOURCE OF NB-UVB[7]

The source of NB-UVB is Philips TL-01 flourescent bulbs that deliver UVB in the range of 310 to 315nm with a peak at 312nm. It has a relatively narrow spectrum of emission and results in a reduction in erythmogenic wavelengths in the 290 to 305nm range and 5 to 6 fold increased emission of longer wavelengths, thereby resulting in a higher phototherapy index for psoriasis.

EFFECTS OF ULTRAVIOLET RADIATION ON SKIN[8]

Interaction of light with the skin results in photobiological reactions.

Photobiological reactions takes place in several steps.

Step 1: Absorption of light by chromophore

For a photobiologic reaction to occur light has to be absorbed by molecules known as chromophores which could be proteins or DNA. Each chromophore absorbs light of specific wavelength, called the absorption spectrum of the chromophore and the wavelength which has the greatest probability of absorption is called the absorption maxima of the chromophore.

Step 2: Excitation to singlet/triplet state

On absorption of light, the chromophore gets excited into singlet and triplet excited states.

Step3: Formation of photoproduct

Though the triplet state is short lived it may initiate a chemical change in the chromophore, transforming it into photoproduct.

Step4: Initiation of biochemical reactions

The photoproducts so formed may initiate complex biochemical reactions like

enzymatic repair , induction of gene products and DNA replication.

Step 5: Cellular response

These biochemical reactions culminate in a cellular response like apoptosis, mitosis and differentiation.

Step 6: Clinical response

The final step is the clinical manifestations of photobiological reaction in the form of erythema, hyperplasia, tumour formation etc.

SKIN PHOTOTYPES[9]

Susceptibility to sunburn in sunlight and tanning ability depends on the skin phototype of the patient.

Skin phototype	Sunburn susceptibility	Tanning ability
I	High	None
II	High	Poor
III	Moderate	Good
IV	Low	Very good
V	Very low	Excellent
VI	Very low	Excellent

MECHANISM OF ACTION OF NB-UVB

1. Antiproliferative effects[10]:

Through induction of DNA photoproducts UVR transiently inhibits cell proliferation.

2. Immunomodulatory effects[11]:

Because of shorter wavelength ,UVB rays have a more superficial depth of penetration within the skin. As a result, UVB primarily affects keratinocytes and langerhan cells. UVB isomerizes epidermal chromophore trans urocanic acid into cis urocanic acid which is responsible for the immunomodulatory effects[12]. Photoimmunologic effects of UVB fall into three categories:

a. Effects on soluble mediators:

Induces release of soluble immunosuppressive mediators from keratinocytes like IL-10 which decreases antigen presenting ability of langerhans cells[13,14,15].

b. Modulation of the expression of cell surface associated molecules:

Modulates expression of adhesion molecules like ICAM-1 which leads to impaired adherence of langerhans cells and T cells.

c. The induction of apoptosis in pathogenetically relevant cells:

Induces apoptosis of T cells and langerhans cells.

Depletes langerhans cells and alters antigen presenting capacity.

Decreases peripheral natural killer cell activity and lymphocyte proliferation in psoriasis[7].

DOSING SCHEDULE

NB-UVB therapy schedule can be tailored according to the patient's skin type and local experience.

There are two regimens that are commonly used to determine the initial dose[7].

1. Involves determination of patient's minimal erythema dose(MED): MED is determined[16] by standard method using either the same irradiation device or different devices with identical emission spectra.

A template with 20 apertures (10 on each side) of 1.5 x1.5 cm^2 is made over the back of a cotton suit used by the operation theatre staff. The cotton flaps over the apertures enable to either shut or keep the apertures open by using Velcro.

All apertures are kept open and back irradiated with 50mJ of NB-UVB. First one aperture is closed and thereafter remaining aperture are closed one after the other after delivering 50mJ more than the previous aperture. The dosing schedule of NB-UVB (in

mJ) is 50, 100, 150, 200, 250, 300, 350, 400, 450, 500.

The readings are taken 24 hours after exposure. MED is that titrated dose that shows well demarcated erythemic response .

The initial dose for NB-UVB should be 70% of MED. Patients are treated 3-5 times a week. Although more sittings will be beneficial, 2-3 sittings are more cost effective and hence more acceptable.If the initial dose is tolerated a 20% incremental increase of the previous dose is used at each visit.

When a previous treatment results in erythema, no treatment is given in next schedule. Increment every second and third sitings is also effective because sub-erythmogenic dose of UVB is also as effective as erythmogenic dose.

2. Another approach commonly practiced in India involves a standard starting dose (280mJ /cm^2) with stepwise increase (usually 20%) depending upon the patient's erythema response.

In case of mild erythema, the irradiation dose is held constant for subsequent treatment or until resolution of symptoms. The goal of therapy is to achieve persistent asymptomatic erythema.

In case of painful erythema with or without edema or blistering further treatment

is withheld till the symptoms subside. After resolution of over dose symptoms, the dose administered is 50% of the last dose and subsequent increments should be by 10%.

In the photodermatoses, the approach is more cautious with only 10% incremental regimen on sun exposure sites.

MAXIMUM DOSE[17]

In responsive patients NB-UVB can be given for a maximum of 24 months. After one year, a resting period of 3 months is recommended to minimize the annual cumulative dose of UVB. In children, the maximum duration allowed is 12 months.

NARROW BAND UVB RESPONSIVE DERMATOSES[18]

COMMON INDICATIONS

1. Psoriasis
2. Vitiligo
3. Atopic dermatitis

OTHER INDICATIONS

1. Mycosis fungoides
2. Parapsoriasis
3. Generalized lichen planus
4. Pityriasis rosea
5. Pruritus

6. Seborrheic dermatitis

7. Pityriasis rubra pilaris

8. Prurigo nodularis

9. Scleroderma

10. Acquired perforating dermatosis

FOR PREVENTION OF PHOTODERMATOSES

Prophylactic low dose NB-UVB is beneficial for photosensitive dermatoses like

1. Polymorphic light eruption

2. Actinic prurigo

3. Hydroa vacciniforme

4. Cutaneous porphyrias

NB-UVB provides a “hardening photo protective” effect. A typical course involves 10-25 treatments given in early spring.

Beneficial role has been observed with airborne contact dermatitis to parthenium hysterophorus, but it is not always effective[19,20].

CONTRA INDICATIONS[7]

ABSOLUTE:

1. Congenital photosensitivity disorders

2. Lupus erythematosus

3. Pemphigus and Pemphigoid

RELATIVE:

1. Concurrent photosensitivity medications

2. Prior exposure to ionizing radiation

3. History of skin cancer or chronic actinic damage

4. Personal or family history of melanoma

5. Persons with skin type 1

6. Unstable, erythrodermic or pustular psoriasis

ADVERSE EFFECTS OF NB-UVB[18]

SHORT TERM:

1. Erythema[21]
2. Pruritus[22]
3. Blistering of psoriatic plaques[23,24]
4. Blepharitis and photokeratitis[25]
5. Recurrent Herpes labialis[26]
6. Photoallergic dermatitis
7. Worsening of disease

LONG TERM:

1. Photoaging
2. Photocarcinogenesis[27]
3. Immunosuppression

ADVANTAGES OF NB-UVB OVER PUVA[7]

1. No oral or topical sensitizing drug needed
2. No drug induced side effects and no drug costs
3. No need for post treatment eye protection
4. Safe in pregnancy and children

ADVANTAGES OF NB-UVB OVER BB-UVB

1. Emits longer UVB wavelengths resulting in a higher phototherapy index for psoriasis and is more effective than BB-UVB[28,29].

2. Less likely to burn[3].

3. NB-UVB is capable of more efficiently depleting skin-infiltrating T cells from the epidermis and dermis of psoriatic plaques as compared with BB-UVB[12].

NB-UVB IN PSORIASIS

NB-UVB lamps emit a narrow UV band at 311/312nm thereby matching the closely assumed therapeutic optimum for psoriasis[4]. NB-UVB phototherapy has a higher therapeutic to erythmogenic ratio resulting in increased efficacy, reduced incidence of burning and longer remission. It is a relatively safe method in the treatment of psoriasis responding poorly to topical treatment, rapidly spreading psoriasis, wide spread psoriasis and severe psoriasis of palms and soles.

COMBINATION THERAPY[7]

Phototherapy may be combined with topical or systemic agents to achieve higher clearance rates, longer disease free intervals and a lower carcinogenic risk[30].

TOPICAL AGENTS: include anthralin, tar, vitamin D analogues, retinoids, glucocorticoids, emollients and salt water baths.

Anthralin and tar are not used frequently.

- The combination of NB-UVB with calcipotriol increases the therapeutic efficacy of phototherapy. UVB reduces the irritation caused by calcipotriol. Vitamin D analogues should be applied after phototherapy, because UV light causes degradation

of vitamin D_3.

- Topical application of emollients applied immediately before exposure to UV radiation alters the optical properties of psoriatic lesions improving UV transmission and increasing efficacy but care should be taken that they do not act as sunscreens.

- Balneotherapy is the combination of salt water baths with UVB phototherapy. Salt water baths are hampered by logistics (the requirement for bath tubs) and environmental concerns related to disposal of large amounts of salt.

SYSTEMIC AGENTS : include retinoids, glucocorticoids, cyclosporine and methotrexate.

- Advantages of combining retinoids and uvb are

1. Retinoids exert antipsoriatic effects and act synergistically

2. They have anticarcinogenic effects and lowers risk due to UVB

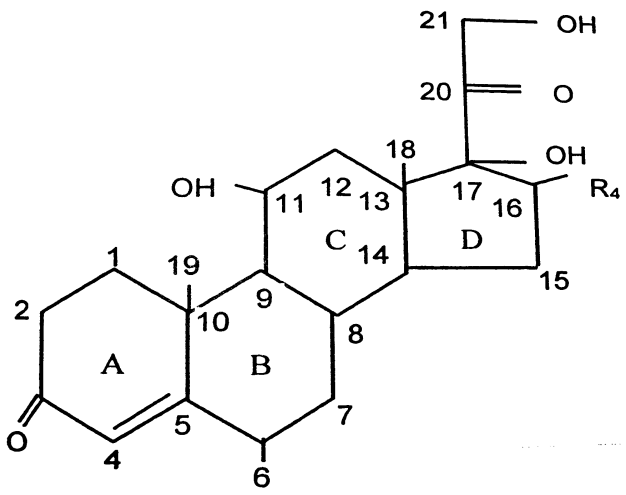
- Systemic steroids in combination with UVB is limited to special indications such as generalized pustular psoriasis.

- Combination regimens of UVB with methotrexate or cyclosporine are used with caution as they may increase the possibility of UV induced skin tumours.

TOPICAL CORTICOSTEROIDS

Topical corticosteroids are the most frequently used drugs in dermatology, since the introduction of hydrocortisone by Sulzberger and Witten in 1952.

STRUCTURE AND CONFIGURATION[31]



Hydrocortisone (cortisol) is the parent compound of all derivatives. It has a cyclopentenoperhydrophenanthrene nucleus. Modification of both the ring structure and the side chains produced dramatic changes in the potency of the steroid. Addition of a hydroxyl or methyl group at the 16th position will increase the efficacy without a concomitant increase in the mineralocorticoid effect. Halogenation at the 9th position, allows improved activity within the target cell and decreased breakdown into inactive metabolites.

CLASSIFICATION[32]

The ability of a given corticosteroid agent to cause vasoconstriction usually correlates with its anti-inflammatory potency and thus, vasoconstriction assays are used to separate the topical corticosteroids into seven classes based on potency.

CLASS 1- SUPERPOTENT

Betamethasone dipropionate 0.05% optimized vehicle

Clobetasol propionate 0.05%

Diflorasone diacetate 0.05%

Fluocinonide 0.1% optimized vehicle

Flurandrenolide, 4mg/cm^2

Halobetasol Propionate 0.05%

CLASS 2 - POTENT

Amcinonide 0.1%

Betamethasone dipropionate 0.05%

Desoximetasone 0.25%

Desoximetasone 0.5%

Diflorasone diacetate 0.05%

Flucinonide 0.05%

Halcinonide 0.1%

Mometasone furoate 0.1%

CLASS 3 – POTENT, UPPER MID STRENGTH

Amcinonide 0.1%

Betamethasone dipropionate 0.05%

Betamethasone valerate 0.1%

Diflorasone diacetate 0.05%

Flucinonide 0.05%

Fluticasone propionate 0.005%

CLASS 4 – MIDSTRENGTH

Betamethasone valerate 0.12%

Clocortolone pivalate 0.1%

Desoximetasone 0.05%

Flucinolone acetonide 0.025%

Flurandrenolide 0.05%

Hydrocortisone probutate 0.1%

Hydrocortisone valerate 0.2%

Mometasone furoate 0.1%

Prednicarbate 0.1%

Triamcinolone acetonide 0.1%

CLASS 5 – LOWER MID STRENGTH

Betamethasone dipropionate 0.05%

Betamethasone valerate 0.1%

Flucinolone acetonide 0.025%

Flurandrenolide 0.05%

Fluticasone propionate 0.05%

Hydrocortisone butyrate 0.1%

Hydrocortisone valerate 0.2%

Prednicarbate 0.1%

Triamcinolone acetonide 0.1%

CLASS 6 – MID STRENGTH

Alclometasone dipropionate 0.05%

Desonide 0.05%

Flucinolone acetonide 0.01%

CLASS 7 – LEAST POTENT

Topicals with dexamethasone, flumethasone, hydrocortisone, methylprednisolone, prednisolone

MECHANISM OF ACTION[32]

Topical steroids exert their effects through both direct and indirect mechanisms which are mediated via the glucocorticoid receptors[33] as follows:

1. Steroid diffuses into the target cells and binds to the glucorticoid receptor in the cytoplasm.

2. Steroid-receptor complex undergoes necessary conformational changes.

3. The resulting active complex traverses the nuclear envelope and binds to specific DNA sequences, the glucocorticoid responsive elements(GRE).

4. Transcription of specific mRNA and regulation of protein synthesis.

The metabolic effects of steroids are generally mediated by transcriptional activity, while the anti-inflammatory effects are mediated by transrepression.

ANTI-INFLAMMATORY ACTION

Steroids exert anti-inflammatory effects by:

- Inhibiting the enzyme phospholipase A_2 by the induction of phospholipase A_2 inhibitory proteins, collectively called lipocortins

- Inhibiting transcription factors(e.g.activator protein 1 and nuclear factor kB) which are involved in the activation of pro-inflammatory genes

- Decreasing the release of IL-1alpha
- Inhibiting phagocytosis
- Stabilizing lysosomal membranes

IMMUNOSUPPRESSIVE EFFECTS

- Steroids suppress the production and effects of humoral factors
- Inhibit leukocyte migration
- Interfere with function of endothelial cells, granulocytes, mast cells, and fibroblasts
- Causes mast cell depletion and decrease the number of Ia langerhan cell
- Reduce T cell proliferation and induce T cell apoptosis

ANTIPROLIFERATIVE EFFECT

This effect is mediated by inhibition of DNA synthesis and mitosis.

VASOCONSTRICTIVE ACTION

This is mediated by inhibition of natural vasodilators such as histamine and bradykinin. Topical steroids cause capillaries in the superficial dermis to constrict thus reducing erythema.

ADVERSE EFFECTS[32,34]

The same mechanism of action responsible for the effectiveness of topical steroids are responsible for their adverse effects[35]. These include

LOCAL SIDE EFFECTS:

- Epidermal atrophy – fragile skin , striae, telangiectasia, stellate pseudoscars, hypopigmentation
- Impaired wound healing
- Steroid rebound
- Contact dermatitis[36]
- Tachyphylaxis
- Glaucoma/cataract
- Facial hypertrichosis
- Folliculitis and miliaria
- Exacerbation and increased susceptibility to bacterial, viral and fungal infections[37]:

    1. crusted scabies
    2. tinea incognito

3. infantile gluteal granuloma

- Perioral dermatitis, rosacea[38] and acneiform eruption

SYSTEMIC SIDE EFFECTS[31]:

- Suppression of hypothalamic-pituitary-adrenal axis
- Iatrogenic Cushing's syndrome
- Growth retardation in children

TACHYPHYLAXIS [37]

Tachyphylaxis describes the diminishing effect of a pharmacological agent when it is repeatedly used to achieve a clinical response. The vasoconstriction response that is seen when first applied to human skin diminishes with subsequent application. Similarly depression of DNA synthesis by topical steroids will also show tachyphylaxis. Topical steroids suppression of histamine whealing has been described in humans. This can be overcome by administering the drug on an intermittent basis.

CONTRAINDICATIONS TO TOPICAL STEROIDS [33]

Absolute

1. Known hypersensitivity to the topical corticosteroids.
2. Known hypersensitivity to a component of the vehicle.

Relative

1. Bacterial, mycobacterial, fungal, viral infection
2. Infestation
3. Ulceration
4. Pregnancy and lactation (Should be used with caution at sites other than the breast or nipple during lactation)

SAFETY PROFILE

PAEDIATRIC USES[39]

Topical glucocorticoids are highly effective and fewer side effects are observed when a low potency preparation is used for brief periods of time without occlusion in children. Infants however are at an increased risk for side effects, likely suppression of endogenous cortisol production leading to addisonian crisis and growth retardation because of thin skin and inability to metabolise potent steroids rapidly.

GERIATRIC USES[40]

Elderly patients can have thin skin, which allows for an increased penetration of topical steroids. Also, they are more likely to have preexisting skin atrophy due to aging and hence precautions are to be taken while giving steroids to elderly. Proper selection based on several factors like anatomical site, potency, dosage form, application technique, coexisting infection and atrophy must be done

USES IN PREGNANCY[32]

Studies on animals shows that when used in excessive amounts, under occlusion for long periods, they are systematically absorbed and can cause fetal abnormalities. It is categorized as 'C' drug by F.D.A. It is unknown whether topical steroids are excreted in breast milk. They should not be used on the breast prior to breast- feeding.

GUIDELINES FOR USE[41]

1. Frequency of application

In most instances, applying twice daily of the more potent steroids will suffice. The use of daily or alternate day therapy should be considered, particularly with extremely potent steroids.

2. Determining the necessary amount

The necessary amount is determined by fingertip unit(FTU) and rule of nine[42,43] . A fingertip unit is the amount of ointment expressed from a tube with a 5mm diameter nozzle, applied from the distal skin crease to the tip of the palmar aspect of the index finger. One FTU weighs 0.49 g in adult males, and 0.43 g in adult females and covers an area of about 300cm^2 . The rule of hand states that an area covered by four adult hands(including digits) can be treated by 1 g of ointment or two FTUs.

3. Potency

Plaque type psoriasis is a relatively steroid resistant dermatoses and often the dermatologist must start with a potent agent. Conversely, psoriasis of the body folds with relatively minimal induration and scaling may be steroid sensitive and respond to a much less potent agent. One can start with mid potent steroid and later the potency can always be increased if the psoriatic plaque fails to respond.

The vasoconstrictor assay is the most commonly employed test to estimate the potency of the topical corticosteroid used.

Combination therapies[30]

Corticosteroids can be combined with the following to increase the efficacy while reducing the incidence of local side effects.

a. Dithranol[44]

b. Calcipotriene[45]

c. Tazarotene[46]

d. Salicylic acid[47]

e. PUVA

f. UVB

g. Oral retinoids

h. Cyclosporine

TOPICAL TAZAROTENE

INTRODUCTION

Retinoid is defined as any molecule that by itself or through metabolic conversion, binds to and activates the retinoic acid receptors, thereby eliciting transcriptional activation of retinoic acid responsive genes that results in specific biological responses[48].

The history of the development of retinoids in dermatology comprise of three generations. The first is non aromatic retinoids, which include tretinoin (retinoic acid) and isotretinoin (13 cis retinoic acid). Both can be used as topical or systemic treatment[49].

The second generation retinoids are monoaromatic retinoids, etretinate and its metabolite acitretin, which are only effective as systemic treatment. The third generation retinoids are polyaromatics, which include. adapalene, tazarotene and bexarotene.

When topical tretinoin was introduced for acne in 1970s, dermatologists also used it to treat psoriasis. Irritation from retinoids was unacceptable and the use of topical retinoids in this setting was never popularized. It was reported that topical tretinoin helped prevent topical corticosteroid atrophy[50]. Subsequently topical retinoids were used

to prevent topical corticosteroid atrophy in patients who are dependent on topical steroids for their psoriasis treatment. The development of tazarotene led to a renewed evaluation of topical retinoid therapy for psoriasis. Tazarotene was developed as an antipsoriatic drug due to the therapeutic results of decreased scaling and plaque thickness[51,52].

RETINOID RECEPTORS

Retinoids affect gene expression by entering the nucleus and binding with two basic type of nuclear receptors belonging to the nuclear receptor superfamily: retinoic acid receptors (RARs) and retinoid X recptors (RXRs)[53]. Each has three specific subgroups: α, β and γ.

These receptors bind to regulatory regions in DNA known as Retinoid response elements or target sequences and activate gene transcription in a ligand dependent manner. Therefore they are referred to as ligand dependent transcription factors[48]. The retinoid receptors are mainly active as heterodimers of RXR and RAR. The end result of these processes acting on numerous different genes is that retinoids demonstrate a tendency to normalize keratinocyte differentiation in diverse circumstances where it is disturbed.

The receptors most abundantly expressed in the epidermis are RAR-γ and RXR-α while RAR-α and RXR-β are relatively present at low levels[54,55].

TAZAROTENE

Tazarotene is a member of the acetylenic retinoids that selectively binds retinoic acid recptors(RARs). Tazarotene is the only topical retinoid useful in psoriasis.

PHARMACOKINETICS

Tazarotene is a prodrug that is hydrolyzed rapidly in tissues to the active metabolite termed tazarotenic acid. Topical tazarotene produces high cutaneous concentrations, but the systemic absorption of the prodrug is practically nonexistent because of its rapid metabolism to tazarotenic acid. Total systemic absorption is up to 5% of the drug applied in normal skin and 15% of the amount applied in psoriatic skin[56,57].

The maximal concentration of tazarotenic acid in the blood occurs 9 hours after tazarotene application. The half life of tazarotene is less than 20 minutes. Small amounts of tazarotene, which are absorbed systemically and not degraded, are excreted in both the urine and feces. The degradation of tazarotenic acid is via oxidation to inactive sulfoxide and sulfone derivatives that are excreted in the urine. The terminal half life of tazarotenic acid is approximately 18 hours[57].

MECHANISM OF ACTION

Tazarotenic acid has a high affinity to the RAR-γ nuclear receptor that is the

predominant receptor present in the epidermis. It also binds to RAR-α and RAR-β but not to RXRs. By binding to the various RARs, tazarotenic acid modulates the expression of retinoid responsive genes, including those that regulate cell proliferation, cell differentiation, and inflammation[58,59]. Tazarotene downregulates the abnormal expression of keratinocyte transglutaminase 1 (Tgase 1), epidermal growth factor receptor, and hyperproliferative keratins K6 and K16[52,60].

It upregulates the expression of three novel genes, tazarotene inducible gene(TIG-1, TIG-2, and TIG-3) in patients with psoriasis, which may mediate an antiproliferative effect[61].

Migration inhibitory factor–related protein (MRP-8), a marker of inflammation, is decreased by tazarotene[61].

It blocks the induction of ornithine decarboxylase activity, which is associated with cell proliferation and hyperplasia[62]. It also inhibits cornified envelope formation and corneocyte accumulation[62].

FORMULATION

Tazarotene is available as both gel and cream, in a concentration of 0.05% and 0.1%. The 0.1% tazarotene gel is approved for both acne and psoriasis whereas the 0.05% tazarotene gel is only approved for psoriasis[63].

EFFICACY OF TAZAROTENE IN PSORIASIS

Tazarotene is indicated in mild to moderate psoriasis. It has a rapid onset of action, indicated by improvement as early as two weeks of treatment[62]. Sustained beneficial effects occur for up to 12 weeks after cessation of therapy. The drug is very effective in reducing plaque thickness and clearing of psoriatic lesions. Psoriatic onycholysis and nail pitting also improves with tazarotene[64]. Tazarotene therapy in psoriasis is limited by its tendency for cutaneous irritation. It is applied as a thin layer over the plaques at bed time and the surrounding normal skin should be protected.

COMBINATIONS[30]

Tazarotene can be combined with topical steroids and phototherapy. The combination with a topical steroid enhances efficacy and tolerability. Use in combination with phototherapy results in greater efficacy than with phototherapy alone.

CONTRAINDICATIONS[62]

1. Pregnancy, lactation and women not practicing adequate contraception
2. Hypersensitivity to tazarotene or the vehicle.
3. Eczematous skin, sunburn and exposure to weather extremes.
4.

ADVERSE EFFECTS

Skin irritation, peeling, erythema, dryness, burning and itching are the common side effects. They occur in up to 30% of patients. It is temporary occurring most commonly during the first 1-2 weeks of theapy and diminishing thereafter. They can be minimized with the use of the cream formulation, alternate day application, short contact therapy, mild cleansers and combination therapies and liberal use of emollients[65].

Decreased tolerance to UV radiation leading to phototoxic reactions can occur. Retinoid dermatitis forming at the periphery of psoriatic plaques and worsening of the diseases with photokoebnerisation can cause discomfort to the patient.

Tazarotene is safe from a systemic point of view. No clinically significant systemic, ophthalmologic, hematologic, or biochemical abnormalities has been reported[56].

SAFETY MEASURES

A pregnancy test is recommended before the use of tazarotene in women of child bearing potential and appropriate birth control measures should be in place for the entire duration of treatment[66].

Concomitant use of irritating topical products such as medicated or abrasive soaps, cosmetics and products with high concentration of alcohol, astringents, spices or lime should be avoided. Also topical products containing sulfur, resorcinol or salicylic acid should be avoided while using topical tazarotene[62].

AIM OF THE STUDY

This study was conducted in patients with chronic plaque type of psoriasis involving less than 20% of body surface area to evaluate the efficacy and safety of

1. Narrow Band UVB

2. Narrow Band UVB with topical betamethasone valerate

3. Narrow Band UVB with topical tazarotene

MATERIALS AND METHODS

Sixty patients who attended the psoriasis out patient clinic at the Department of Dermatology, Government General Hospital, Chennai from August 2007 to September 2009 were included in the study.

The diagnosis of psoriasis was made on clinical grounds and histopathological examination.

SELECTION CRITERIA

Patients with chronic plaque type of psoriasis involving less than 20% of the body surface area.

EXCLUSION CRITERIA

1. Photosensitive disorders or history of photodamage
2. Previous or family history of malignant melanoma
3. History of exposure to inorganic arsenic or ionizing radiation
4. Past history of internal or skin malignancy
5. Pregnant and lactating women
6. Women contemplating conception

All patients were explained about the disease and the benefits and side effects of the treatment were discussed with them.

Consent was obtained from all patients before initiation of treatment.

All patients were evaluated as follows:

1. History
2. General examination
3. Systemic examination
4. Dermatological examination
5. Investigations

a. Complete haemogram

b. Urine analysis

c. Blood sugar, urea, serum creatinine, calcium and uric acid

d. Liver function tests

e. Blood VDRL

f. ELISA for HIV

g. Ophthalmic evaluation

TREATMENT PROTOCOL AND METHODOLOGY:

Sixty patients with chronic plaque type of psoriasis involving less than 20% of body surface area were randomly allocated to any one of the following three groups

Group A: Narrow Band UVB phototherapy

Group B: Narrow Band UVB with topical betamethasone valerate

Group C: Narrow Band UVB with topical tazarotene

GROUP A: NB-UVB GROUP

- 20 Patients were included in this study.
- All patients were asked to wear UV goggles when inside the phototherapy unit.
- Men were advised to protect their genitalia.
- Patients were asked to apply liquid paraffin oil on the plaques of psoriasis prior to exposure.
- As all patients were of skin types IV and V, initial UVB dose of 250 mJ/cm^2 was started in all patients.
- The manual method for calculation of time (seconds) to set UVB control panel to deliver the dose is by the following equation.

Time (seconds) = Dose (mJ/cm^2) / Irradiance (mw/cm^2)

- Patients were advised to expose only the affected parts during treatment and protect other uninvolved areas.
- Patients were instructed to come out of the chamber when the light switches off or if they became uncomfortable during the treatment either due to burning or stinging sensation of the skin.
- If the initial dose was tolerated, subsequent 20% incremental dose was given at each subsequent visit depending on the patient's erythema response.
- Treatment was given thrice weekly on non consecutive days.
- Patients were monitored regularly every week.
- Patients were instructed to report immediately if any of the adverse effects were noted.

GROUP B: NB-UVB WITH TOPICAL BETAMETHASONE

- 20 patients were included in this study.
- Patients were advised to apply 0.1% betamethasone valerate ointment once daily at bed time.
- Patients were asked to apply the ointment in a thin layer only over the plaques.
- Patients received Narrow Band UVB phototherapy thrice weekly similar to patients in group A in addition to topical betamethasone valerate once daily.
- Patients were monitored regularly every week.
- Patients were asked to report immediately if any of the adverse effects were noted.

GROUP C: NB-UVB WITH TOPICAL TAZAROTENE

- 20 patients were included in this study.
- Patients were asked to apply 0.1% tazarotene cream once daily at bed time.
- Patients were asked to apply the cream in a thin layer only over the plaques.
- Patients received Narrow Band UVB phototherapy thrice weekly similar to patients in group A in addition to topical tazarotene once daily at bed time.

- Patients were regularly monitored every week.
- Patients were instructed to report immediately if any of the adverse effects were noted.

Efficacy Assessment

Severity and extent of psoriasis were evaluated using “Psoriasis Area and Severity Index” (PASI).

Severity of Erythema (E), Desquamation (D) and Induration (I) was recorded on a 5 point scale as follows:

0	-	Nil
1	-	Mild
2	-	Moderate
3	-	Severe
4	-	Very Severe

The area of involvement was recorded on a 7 point scale as follows:

0	-	Nil
1	-	< 10 %
2	-	10 % - 29 %
3	-	30 % - 49 %
4	-	50 % - 69 %

5 - 70 % - 89 %

6 - 90 % - 100 %

PASI was calculated as follows

PASI = $0.1 (E_H + I_H + D_H) A_H + 0.2 (E_U + I_U + D_U)A_U +$

$0.3 (E_T + I_T + D_T) A_T + 0.4 (E_L + I_L + D_L)A_L$

A - Area

H - Head

U - Upper Limb

T - Trunk

L - Lower Limb

OBSERVATIONS AND RESULTS

Age distribution (Fig.1)

The mean age in our study was 36.71. The range was from 14 to 76 years.

Sex distribution (Fig 2, Table 1)

Males outnumbered females in each of the three groups. The overall male to female ratio was observed to be 57% : 43%

Table 1(n=60)

Sex	NB-UVB	Betamethasone combination	Tazarotene combination
Male	11	11	12
Female	9	9	8

Duration of illness (Fig 3)

The mean duration of illness was 42.4 months. The range was from 3 months to 120 months.

Family history

Family history was not present in any of the patients in our study.

Nail changes (Fig 4) Totally 27(45%) patients had nail involvement, out of which 19(32%) patients had nail pitting

4 patients (7%%) had ridging

3patients (5%) had subungual hyperkeratosis

4 patients(7%) had onycholysis some patients had more than one nail changes.

Joint involvement

Four patients in our study had joint involvement, 1 in Narrowband UVB group, 2 in betamethasone combination group and 1 in tazarotene combination group in the form of asymmetrical oligoarthritis.

PASI reduction

The following graphs and tables show the reduction of PASI scores from baseline, at 4 weeks, 8weeks, 12weeks and 16 weeks in NB-UVB group and betamethasone combination group (Fig 5, Table2) and NB-UVB group and tazarotene combination group (Fig 6, Table3).

Percentage of PASI reduction

The following graphs and tables show the reduction of PASI in percentages at baseline, 4 weeks , 8 weeks, 12 weeks and 16 weeks in NB-UVB group and betamethasone combination groups (Fig.7, Table 4) and NB-UVB group and tazarotene combination groups (Fig.8, Table 5).

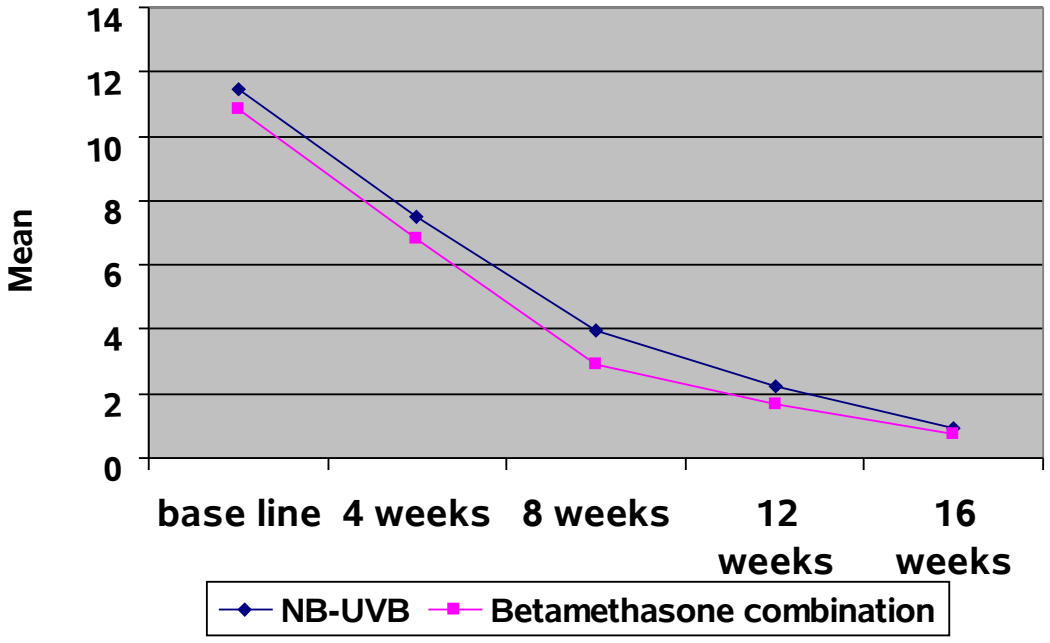
From figures 5,7 and tables 2,4 we can see that the baseline PASI scores for the NB-UVB group and betamethasone combination groups are 11.48 and 10.87. There is no statistically significant difference ($p>0.05$) in baseline PASI among NB-UVB group and betamethasone combination group. There is a decrease in PASI scores at 4, 8, 12 and 16 weeks to 7.47, 3.96, 2.26, 0.92 and 6.83, 2.9, 1.69 and 0.74 with respect to NB-UVB group and betamethasone combination group. This corresponds to a percentage reduction to 34.9%, 65.5%, 80.3% and 91.9% in NB-UVB group and 37.1%, 73.3%, 84.4% and 93.1% in betamethasone combination group. Here there is no statistically significant difference in PASI at 4, 8, 12 and 16 weeks ($p>0.05$).

PASI REDUCTION

Table 2

Duration	MEAN PASI SCORE	
	NB-UVB	Betamethasone Combination
Baseline	11.48	10.87
4 weeks	7.47	6.83
8 weeks	3.96	2.9
12 weeks	2.26	1.69
16 weeks	0.92	0.74

Fig. 5

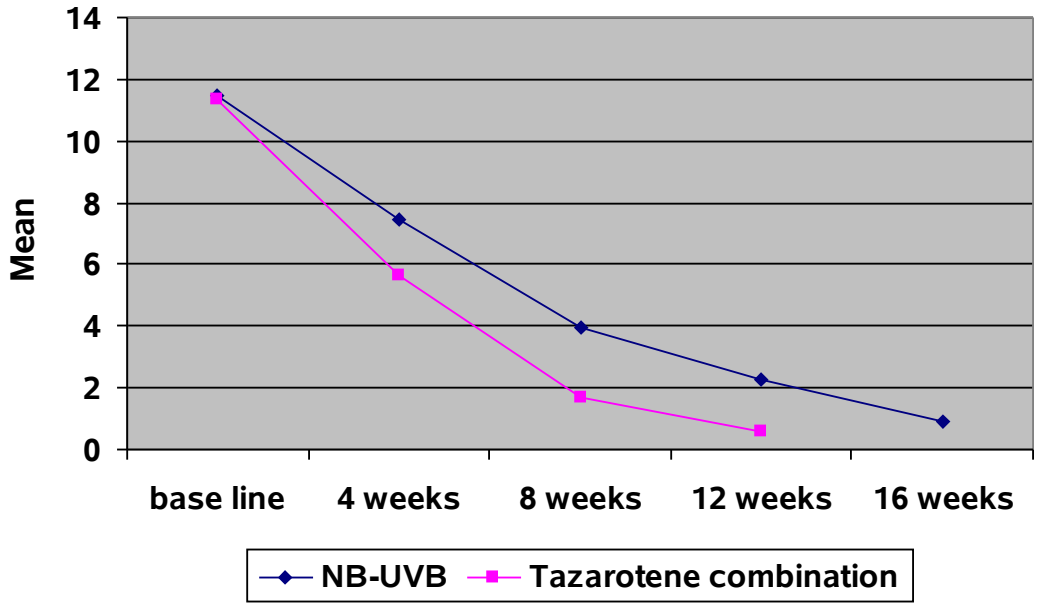


PASI REDUCTION

Table 3

Duration	MEAN PASI SCORE	
	NB-UVB	Tazarotene Combination
Baseline	11.48	11.32
4 weeks	7.47	5.64
8 weeks	3.96	1.70
12 weeks	2.26	0.57
16 weeks	0.92	

Fig. 6



PERCENTAGE REDUCTION IN PASI

Table 4

Duration	NB-UVB	Betamethasone Combination
Baseline	0	0
4 weeks	34.9	37.1
8 weeks	65.5	73.3
12 weeks	80.3	84.4
16 weeks	91.9	93.1

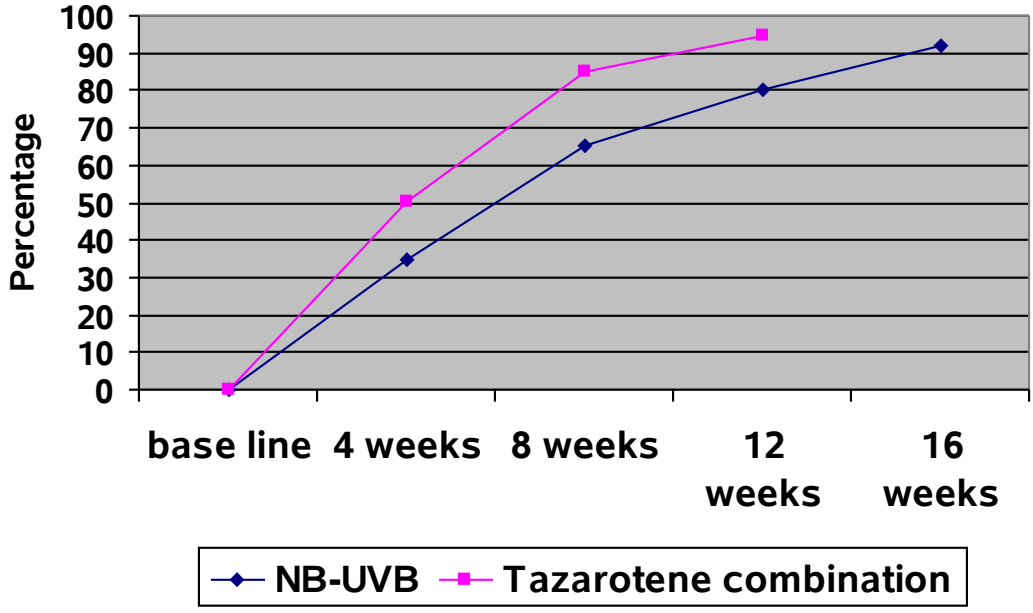
Fig. 7

PERCENTAGE REDUCTION IN PASI

Table 5

Duration	NB-UVB	Tazarotene Combination
Baseline	0	0
4 weeks	34.9	50.1
8 weeks	65.5	84.9
12 weeks	80.3	94.9
16 weeks	91.9	

Fig. 8



From figures 6, 8 and tables 3, 5 we can see that the mean baseline PASI scores for NB-UVB group and tazarotene combination group are 11.48 and 11.32 respectively. There is no statistically significant difference ($p>0.05$) in baseline PASI among NB-

UVB group and tazarotene combination group . At 4 weeks, PASI scoring has reduced to 7.47 and 5.64 respectively for the above mentioned groups. Thus there is more than 50% reduction in the tazarotene combination group whereas only 34.9% reduction in NB-UVB group. There is a further fall in PASI scoring at 8 weeks to 3.96 and 1.70 in NB-UVB group and tazarotene combination groups which correspond to reduction in percentages of 65.5% and 84.9% respectively. A further reduction in PASI score is observed at 12 and 16 weeks to 2.26 and 0.92 in the NB-UVB group which corresponds to a percentage reduction to 80.3% and 91.9%. In the tazarotene combination group, the reduction in PASI is more rapid with mean PASI score of 0.57 at 12 weeks corresponding to a percentage reduction of 94.9%. There is a statistically significant difference ($p<0.05$) in PASI between NB-UVB and tazarotene combination group at 4, 8 and 12 weeks.

Duration of treatment and mean cumulative dose

The mean cumulative dose, average number of exposures and total duration of treatment are tabulated.

Table 6

	GroupA (NB-UVB)	**GroupB (Betamethasone combination)**	**GroupC (Tazarotene combination)**
Average number of exposure	34.8	33.7	25.2
Duration of treatment(weeks)	11.6	11.5	8.8
Mean cumulative dose (J/cm^2)	43.3	40.2	25.1

Response to therapy Based on the percentage reduction in PASI the results were graded as excellent (100%), good (75-100%), moderate (50-75%) and poor(<50%). The results seen in our study has been tabulated (Table7,8 &9).

Group A (NB-UVB)

Table 7

Result	No. of patients	Percentage	% reduction in PASI score at 16 weeks
Excellent	10	53	100
Good	6	31	75-100
Moderate	1	5	50-75
Poor response	2	11	<50

In group A-

Out of 20 patients, 10 patients had complete clearance, 6 patients had good response and 1 had moderate response. 2 patients had poor response and 1 patient discontinued therapy due to unknown reasons.

Group B (NB-UVB with topical betamethasone)

Table 8

Result	No. of patients	Percentage	% reduction in PASI score at 16 weeks
Excellent	12	63	100
Good	4	21	75-100
Moderate	1	5	50-75
Poor response	2	11	<50

In group B-

Out of 20 patients, 12 patients had complete clearance, 4 had good response, 1 had moderate response and 2 had poor response. One patient discontinued treatment due to unknown reasons.

Group C (NB-UVB with topical tazarotene)

Table 9

Result	**No. of patients**	**Percentage**	**% reduction in PASI score at 12 weeks**
Excellent	15	88	100
Good	1	6	75-100
Moderate	1	6	50-75
Poor response	-	-	<50

In group C-

Out of 20 patients, 15 patients had complete clearance, 1 patient had good response and 1 patient had moderate response. Three patients discontinued treatment due to unknown reasons.

Adverse effects (Table 10)

Adverse effects noted in our study has been tabulated.

Table 10

Adverse effect	Group A	Group B	Group C
Pruritus	2	1	1
Erythema	1	1	2
Initial exacerbation	1	1	1
Irritation	0	0	4

Pruritus and erythema was noted in all the three groups. Initial exacerbation was noticed in one patient in each group and it gradually resolved with continuation of the therapy.

Irritation was seen in 4 patients in the tazarotene combination group. It was mild and resolved with liberal use of emollients.

DISCUSSION

At the present time, phototherapy with narrow band UVB is considered one of the most effective therapeutic modalities for patients with psoriasis. Many studies have documented improved efficacy and therapeutic index for narrowband UVB. However, the long term side effects of narrowband UVB therapy have not been fully documented. As a result, there has been a great deal of interest in photocombination therapies that are capable of both reducing cumulative UVB doses and accelerating resolution of skin lesions. To gain our experience, this study was designed to compare NB-UVB therapy with a combination of NB-UVB and topical agents.

TREATMENT RESPONSE

In group A (NB-UVB), the mean baseline PASI score was 11.48 and the mean PASI score at the end of 16weeks was 0.92. There was 91.9% reduction in PASI score at the end of 16 weeks. 10 patients showed complete clearance and 6 patients showed more than 75% clearance. The side effects were also few and treated symptomatically. This shows that NB-UVB is highly effective and safe in psoriasis. Though our study was of low number, the results were consistent with the previous studies[21,67].

Group A (NB-UVB) was compared with group B (NB-UVB with betamethasone valerate) and group C (NB-UVB with tazarotene). The final evaluation involved comparison of both treatments according to the response, cumulative dose and adverse

effects. The response of the patients ranged from excellent (complete clearance) to poor response(<50% decrease in PASI score). In our study, the basic demographic data in all the three groups were similar.

When NB-UVB group was compared with NB-UVB and betamethasone combination group, there was no significant difference ($p>0.05$) in PASI scores at 4, 8, 12 and 16 weeks. The mean duration of treatment was 11.6 weeks in the NB-UVB group and 11.5 weeks in the NB-UVB with betamethasone group. The mean cumulative dose of NB-UVB in our study was 43.3J/cm^2 in NB-UVB group and 40.2J/cm^2 in NB-UVB with betamethasone group. This explains that there is no significant difference between these two groups with respect to PASI reduction, duration of treatment and the mean cumulative dose. .

According to literature and previous studies[10,68,69] done, use of topical steroids with UVB does not add much long term benefit. In our study also, although there was some initial reduction in thickness and a rapid initial response, there was no difference in the duration of treatment and the mean cumulative dose when compared to NB-UVB alone.

When NB-UVB group was compared with NB-UVB and tazarotene combination group, there was a significant difference ($p<0.05$) in PASI scores at 4weeks, 8 weeks and 12 weeks. At 4 weeks, there was more than 50% reduction in PASI in the tazarotene combination group and only 34.9% reduction in NB-UVB group. There was further reduction to 84.9% and 94.9% at the end of 8 weeks and 12 weeks respectively in the

tazarotene combination group while there was only 65.5% and 80.3% reduction at 8weeks and 12 weeks respectively in the NB-UVB group. This explains that there was a rapid fall in PASI score in tazarotene combination group. The mean duration of treatment was 8.8 weeks in the tazarotene combination group and 11.6 weeks in the NB-UVB group. The mean cumulative dose was 25.1J/cm^2 in tazarotene combination group and 43.3J/cm^2 in the NB-UVB group. This explains that tazarotene combination group showed a faster clearance with a lesser cumulative dose.

Koo et al reported that tazarotene plus NB-UVB phototherapy is significantly more effective than NB-UVB phototherapy alone for the treatment of psoriasis and mean cumulative UVB exposure required is significantly lower when tazarotene was combined[70]. The same observations were reported by Behrens et al[71]. In our study also, tazarotene combination proved to be more effective than NB-UVB monotherapy and achieved faster clearance with lesser cumulative dose.

POOR RESPONSE

Poor response was seen in 2 patients each in the NB-UVB group and NB-UVB with betamethasone groups. It correlates with the long duration of illness and it has no correlation with PASI score at the initiation of therapy.

SIDE EFFECTS

The adverse effects in our study were minimal and none of the patients required discontinuation of therapy. In our study, the common side effects noted were pruritus, erythema and initial exacerbation . The adverse effect profile observed in our study was similar to that reported in the literature.

Significant erythema was noted in only 4 of our patients, one each in NB-UVB group and NB-UVB with betamethasone group and 2 in tazarotene combination group but according to literature and other western studies[9,21] the common side effect of UV therapy is erythema. This significant difference is probably because all our patients are of skin type IV and V.

Initial exacerbation was noted in 3 of our patients, one in each group but newer lesions ceased to appear with continuation of therapy. This could be due to immunomodulatory effect of NB-UVB.

Pruritus was noted in 4 of our patients initially which subsided with regular use of emollients and continuation of therapy. It is assumed to be related to prostaglandin release.

Irritation was the common side effect noted in the tazarotene combination group in the previous studies[70,71] and also in our study but it was very mild and managed with liberal use of emollients. Tazarotene combination was well tolerated, with only 3 patients discontinuing therapy due to unknown reasons.

CONCLUSION

- Narrow Band UVB phototherapy is an effective modality of treatment in plaque type of psoriasis.
- Narrow Band UVB is safe and well tolerated in our patients with very few side effects.
- Combining NB-UVB phototherapy and topical betamethasone valerate confers little advantage in treating psoriasis and appears to have no substantial effect on the time to clearing or the mean cumulative dose.
- Combination of tazarotene and NB-UVB phototherapy is significantly more effective than NB-UVB phototherapy alone for the treatment of psoriasis.
- The addition of tazarotene to NB-UVB therapy promotes faster clearing of psoriasis when compared with NB-UVB monotherapy.
- The cumulative dose of NB-UVB is reduced when tazarotene is combined with it which means a lower risk for long term complications.
- Irritation due to tazarotene is mild and combination of tazarotene with NB-UVB is well tolerated.

- Photocombination therapies can broaden the therapeutic options for the treatment of patients with psoriasis.

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PROFORMA

Name: Date:

Age/Sex: OP No:

Occupation: Case No:

Address:

HISTORY
Duration:

Itching : Yes No

H/O Previous treatment : Topical Systemic

EXACERBATION WITH:

Cold climate	Sunlight	Dialysis
Infection	Trauma	Emotional factors
Puberty	Pregnancy	Menopause

PAST HISTORY

Hypertension	Diabetes	Tuberculosis
Photosensitivity	Cutaneous malignancy	Radiotherapy

Drugs taken for any other condition : Yes No

Name of the drug:
Duration of treatment:

FAMILY HISTORY **:** Mother Father
Sibling Others

PERSONAL HISTORY **:** Alcohol Smoking

Menstural history:

Pregnancy Lactation

GENERAL EXAMINATION:

Pallor Icterus Edema
Pulse : BP: Weight:

SYSTEMIC EXAMINATION:

CVS:

RS:

P/A:

CNS:

ENT:

Dental:

DERMATOLOGICAL EXAMINATION:

Skin lesions: Site
Morphology
Surface area involved
Auspitz sign: Yes/No

Mucous membrane:

Palms and soles:

Scalp:

Hair:

Nail:

Joint involvement:

Area and severity assessment by PASI scoring:

Erythema/Infiltration/Desquamation Scoring			Area Scoring
0	-	Nil	0 – Nil
1	-	Mild	1 – 0%-9%
2	-	Moderate	2 – 10 % - 29%
3	-	Severe	3 – 30 % - 49 %
4	-	Very Severe	4 – 50 % - 69 %
			5 – 70 % - 89 %
			6 – 90 % - 100 %

$$PASI = 0.1 (E_H + I_H + D_H) A_H + 0.2 (E_U + I_U + D_U) A_U$$
$$0.3 (E_T + I_T + D_T) A_T + 0.4 (E_L + I_L + D_L) A_L$$

INVESTIGATIONS:

Ophthalmological examination:

Skin Biopsy:

Haemoglobin:

Total count:

Differential count:

ESR:

Blood sugar:

Urea:

Creatinine:

Serum calcium:

Uric acid:

Blood VDRL:

HIV:

LFT:

NB-UVB chart:

Date	Cycle	Dose	Duration	Cumulative dose	Side effects

FOLLOW UP:

Weeks	PASI Score	Cumulative dose
0		
4		
8		
12		
16		

KEY TO MASTER CHART

F	-	Female
M	-	Male
Mon	-	Months
Yrs	-	Years
P	-	Pitting
R	-	Ridging
SUH	-	Sub ungual hyperkeratosis
O	-	Onycholysis
Y	-	Yes
AO	-	Asymmetrical oligoarthritis
PASI	-	Psoriasis Area and Severity Index
SE	-	Side effects
PR	-	Prurritus
IE	-	Initial exacerbation
E	-	Erythema
IR	-	Irritation

ABBREVIATIONS

UVB	-	Ultra violet B
NB-UVB	-	Narrow band ultra violet B
BB-UVB	-	Broad band ultra violet B
UVA	-	Ultra violet A
MED	-	Minimal erythema dose
RAR	-	Retinoic acid receptor
RXR	-	Retinoid X receptor
PASI	-	Psoriasis Area and Severity Index