A STUDY ON THE EFFICACY AND ADVERSE EFFECTS OF IMMUNOSUPPRESSANT DRUGS IN CHRONIC SKIN DISEASES.

DISSERTATION SUBMITTED FOR THE DEGREE OF

M.D BRANCH – VI

PHARMACOLOGY

APRIL – 2015

THE TAMIL NADU

Dr. M.G.R MEDICAL UNIVERSITY

CHENNAI, TAMIL NADU.

Madurai

.09.2014

CERTIFICATE

This is to certify that the dissertation entitled **"A STUDY ON THE EFFICACY AND ADVERSE EFFECTS OF IMMUNOSUPPRESSANT DRUGS IN CHRONIC SKIN DISEASES"** is a bonafide record of work done by **DR.S.YESODHA**, under the guidance and supervision of Dr**. M.SHANTHI M.D.**, Professor, in the Institute of Pharmacology, Madurai Medical College, Madurai during the period of her postgraduate study of M.D Pharmacology from 2012-2015.

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DECLARATION

I, **DR.S.YESODHA** solemnly declare that the dissertation titled **"A STUDY ON THE EFFICACY AND ADVERSE EFFECTS OF IMMUNOSUPPRESSANT DRUGS IN CHRONIC SKIN DISEASES"** has been prepared by me under the able guidance and supervision of **Dr.R.PARAMESWARI. M.D,** Director and Professor, Institute of Pharmacology, Madurai Medical College, Madurai, in partial fulfillment of the regulation for the award of M.D Pharmacology degree examination of the Tamilnadu Dr. MGR Medical University, Chennai to be held in April 2015.

This work has not formed the basis for the award of any degree or diploma to me, previously from any other university to anyone.

Place: Madurai **Dr. S.YESODHA**

Date:

ACKNOWLEDGEMENT

I am greatly indebted to **Capt.Dr.B.Santhakumar**,MSc (F.Sc), M.D (F.M), PGDMLE, D.N.B(F.M),. Dean, Madurai Medical College and Govt Rajaji hospital, Madurai who initiated this interdisciplinary work with generous permission.

It is with great pleasure I record my deep respects, gratitude and indebtedness to **Dr.R.Parameswari** M.D., Director and Professor, Institute of Pharmacology, Madurai medical college, Madurai for her remarkable guidance, encouragement and selfless support which enabled me to pursue the work with perseverance**.** Her contagious enthusiasm was a source of energy to me in successfully completing my dissertation under her generous guidance.

I am extremely thankful to **DR. M.Shanthi** M.D., Professor of Pharmacology, for her valuable suggestions and critical review at every stage for the successful completion of this study.

I am extremely thankful to **Dr. S.Vijayalakshmi** M.D., Professor of Pharmacology, who rendered her able guidance and suggestions to complete my work.

I am thankful to **Dr. R.Sarojini** M.D., Professor of Pharmacology, for her valuable suggestions and support.

I am thankful to **Dr. K.Raadhika** M.D., Associate Professor of Pharmacology, for her valuable suggestions and support.

I am extremely thankful to **Dr. S.Tamilarasi** M.D. Professor of Institute of Pharmacology (Rtd), Madurai Medical College, Madurai for her untiring support, continuous suggestions and enduring encouragement throughout the study.

I wish to express my sincere thanks to **Dr. A.S.Krishnaram** M.D, Professor, Former Head of Department, Department of Dermatology, Madurai Medical College and Government Rajaji Hospital, Madurai for the generous permission and complete co-operation to carry out the study.

I am thankful to **Dr.G.Geetharani** MD, Professor & HOD, Department of Dermatology, Madurai Medical College and Government Rajaji Hospital, Madurai for her kind support and encouragement throughout the study.

I am thankful to **Dr. A.K.P.Vijayakumar** M.D., Associate Professor of Dermatology, for his valuable suggestions and support.

I am thankful to **Dr. M.Saleem** M.D., Associate Professor& Director in charge, Institute of community Medicine, Madurai Medical College, Madurai for his valuable help in Statistics.

I am thankful to **Dr. S.Priya** M.D., Assistant Professor, Institute of community Medicine, Madurai Medical College, Madurai for her valuable help in Statistics.

It is with deep sense of gratitude, I wish to express my sincere thanks to Assistant Professors **Dr.M.S.Ahil** M.D., **Dr.K.Geetha** M.D., **Dr.V.Thaivanai** MD., **Dr.M.Sheik Davooth** M.D., **Dr. M.Malathi** M.D., **Dr. R.Navajothi** M.D, Dr**. S.Sidhaarthan** M.D.

It is my duty to express my appreciation to my colleagues **Dr.K.C.SaravanaKumar, Dr.M.Mathivani, Dr. T.Gowrithilagam, Dr. N.Ajay Kumar, Dr.T.Nivethitha, Dr.B.Bhuvaneswari, Dr. A.Abdulrahman, Dr.J.Arun Kumar, Dr.M.Vijayalakshmi, Dr.S.Vasanth, Dr.G.Muthukavitha, Dr.R.Vijaya Rani, Dr.R.Mangla devi, Dr.S.Kiruthika, Dr.C.Uma maheshwari** for their assistance.

I thank my family members for their kind support and encouragement throughout the study.

Finally I thank the almighty for giving me the courage to complete the study and the patients for their cooperation.

CONTENTS

A STUDY ON THE EFFICACY AND ADVERSE EFFECTS OF IMMUNOSUPPRESSANT DRUGS IN CHRONIC SKIN DISEASES

AIM:

Chronic skin diseases include autoimmune diseases like psoriasis, pemphigus vulgaris and systemic sclerosis which require long term drug therapy. The present study was undertaken to monitor the efficacy and adverse effects of immunosuppressant drugs used in chronic skin diseases.

MATERIALS AND METHODS:

80 newly diagnosed chronic skin diseases patients were included for the study after obtaining ethical clearance. They were started on Methotrexate, Dexamethasone - Cyclophosphamide pulse therapy, Azathioprine, folic acid, calcium and antiulcer agents. Response was assessed by at the end of first, third and sixth month of therapy. In patients with psoriasis the treatment efficacy was monitored by Psoriasis Area Severity Index (PASI) score. In patients with pemphigus vulgaris the treatment efficacy was monitored by Pemphigus Area and Activity Score (PAAS) and in patients with systemic sclerosis the treatment efficacy was monitored by modified Rodnan's skin scores (MRSS). Tolerability was assessed by haematological and clinical examinations.

RESULTS:

Of 80 patients who completed the study 45% were males and 55% were females. The mean age of diagnosis was 38.69 ± 10.67 years. There was statistically significant ($p < 0.0001$) reduction in the PASI Score, PAAS, MRSS at the end of first, third and sixth month of therapy, which showed better response to drug therapy. The adverse effects observed in the study are nausea, vomiting, gastritis, microcytic anaemia and others. These adverse effects were managed by anti emetics, proton pump inhibitors, folic acid, iron supplementation and calcium.

CONCLUSION:

From this study we conclude that extensive use of conventional daily steroids often results in disabling and life threatening adverse effects. The concomitant uses of immunosuppressant drugs like methotrexate, dexamethasone – cyclophosphamide pulse therapy were well tolerated and efficacious in autoimmune skin diseases.

KEY WORDS:

Psoriasis, pemphigus vulgaris, systemic sclerosis, methotrexate, dexamethasone – cyclophosphamide pulse therapy

INTRODUCTION

The normal skin is a major physiological barrier to most microorganisms[1]. In patients with chronic skin diseases the epidermal barrier function is disrupted and the concentration of antimicrobial peptides may be reduced.

Skin diseases are extremely common affecting up to 20 to 30% of individuals at any one time in the general population. Chronic skin diseases includes autoimmune diseases like psoriasis, bullous disorders, systemic sclerosis, systemic lupus erythematosus, dermatomyositis and inflammatory dermatoses like atopic and seborrheic dermatitis[2].

Autoimmune diseases are the result of specific immune responses directed against structures of self. Paul Ehrlich at the beginning of the twentieth century postulated that an immune- mediated mechanism capable of selectively affecting structures of the self was incompatible with life and defined it as 'horror autotoxicus'[3].

Many autoimmune diseases are more common among women than men. It starts at a relatively young age and continue throughout life. Most of the diseases are chronic in nature requiring a life time care. A combination of genetic predisposition and environmental factors contribute to the development of autoimmune diseases[4].

A common feature of all autoimmune diseases is the presence of auto antibodies and inflammation, including mononuclear phagocytes, auto

reactive T lymphocytes and plasma cells. It can affect almost any part of the body, including the heart, brain, nerve, muscles, skin, eyes, joints, lungs and kidneys.

Autoimmune skin diseases are managed with corticosteroids in the early days. The extensive use of steroids often results in disabling and life threatening adverse effects which includes growth retardation in children, poor wound healing, cataract, hyperglycaemia, hypertension, increased incidence of cerebro vascular & cardio vascular diseases due to atherosclerosis.

The concomitant use of immunosuppressive agents have reduced the steroid usage in these diseases and are associated with better treatment outcome and decreased adverse effect of both the drugs. The drugs used are methotrexate, cyclophosphamide, azathioprine & dexamethasone.

Methotrexate has been used in patients with psoriasis which is a common and chronic immune mediated skin disorder. It is a folic acid antagonist interfering with purine pathway and the mechanism of action in psoriasis is immune modulation and anti inflammation[5].

Dexamethasone – Cyclophosphamide pulse therapy seems to have the following advantages over the treatment with steroids alone. (i.e.) better control of disease, nearly absence of steroid side effects and hospital stay is shortened. This regimen has been successfully used as curative treatment in pemphigus, systemic lupus erythematosus, systemic sclerosis and

dermatomyositis. Azathioprine can be used as alternative to cyclophosphamide in bullous disorders.

Even though immunosuppressive therapy has resulted in better treatment outcome, they also have severe adverse effects like bone marrow suppression, decreased immune response, and haemorrhagic cystitis. So this study aims at monitoring the clinical response of south Indian patients with chronic skin diseases attending a tertiary care hospital, along with monitoring the tolerability and safety of Immunosuppressive therapy in the above patients.

AIMS

&

OBJECTIVES

AIM OF THE STUDY

1. To assess the efficacy of drugs used in treatment of autoimmune skin diseases like psoriasis, pemphigus vulgaris and systemic sclerosis.

2. To assess the tolerability of drugs among south Indian population suffering from autoimmune skin diseases.

REVIEW OF LITERATURE

REVIEW OF LITERATURE

AUTOIMMUNE DISEASES

Autoimmune diseases are the result of specific immune responses directed against structures of the self. Autoimmunity is a condition in which structural or functional damage is produced by the action of immunologically competent cells or antibodies against the normal components of the body[6]. Autoimmunity literally means 'protection against self' but it actually implies 'injury to self'. Ehrlich (1901) observed that goats produce antibodies against erythrocytes from other goats but not against their own, and postulated the concept of 'horror autotoxicus'.

EPIDEMIOLOGY

The overall estimated prevalence of autoimmune diseases is 4.5%, among them 2.7% are males and 6.4% are females. The most common mean age for all diseases is 40-50 years[7]. Individual autoimmune diseases are uncommon, among them 5-8% of the population in the United States are affected and are the third most common group of disease in developed countries following cardiovascular disease and cancer.

PATHOGENESIS OF AUTOIMMUNITY

The mechanism by which the immune tolerance of the body is broken causes autoimmunity. These mechanisms of autoimmunity may be immunological, genetic and microbial, all of which may be interacting[8,9].

1. **Immunological factors**

Failure of immunological mechanisms of tolerance initiates autoimmunity. These mechanisms are as follows:

i) Polyclonal activation of B cells. B cells may be directly activated by stimuli such as infection with microorganisms and their products leading to bypassing of T cell tolerance.

ii) Generation of self-reacting B cell clones may also lead to bypassing of T cell tolerance.

iii) Decreased T suppressor and increased T helper cell activity. Loss of T suppressor cell and increase in T helper cell and activities may lead to high levels of auto-antibody production by B cells contributing to auto-immunity.

iv) Fluctuation of anti-idiotype network control may cause failure of mechanisms of immune tolerance.

v) Sequestered antigen released from tissues. Self-antigen which is completely sequestered may acts as foreign-antigen if introduced into circulation later.

2. **Genetic factors**

There is evidence in support of genetic factors in the pathogenesis of autoimmunity as under:

i) There is increased expression of Class II HLA antigens on tissues involved in autoimmunity[10,11].

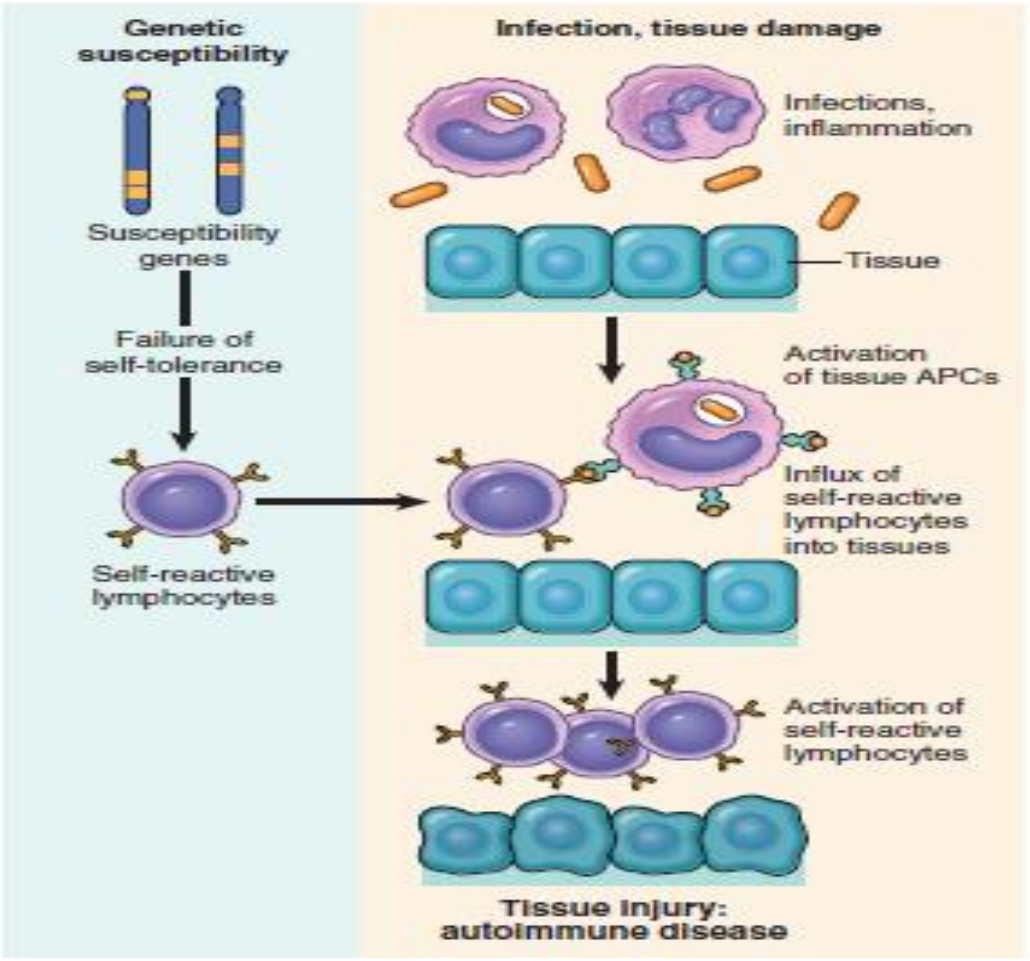
ii) There is increased familial incidence of some of the autoimmune disorders.

3**. Microbial factors**

Infection with microorganisms, particularly viruses (e.g. EBV infection) and less often bacteria (e.g. streptococci, Klebsiella) and mycoplasma, has been implicated in the pathogenesis of autoimmune diseases (Figure1).

FIGURE 1

PATHOGENESIS OF AUTOIMMUNE DISEASES



GENERAL FEATURES OF AUTOIMMUNE DISEASES

- Once an autoimmune disease has been induced it tends to be progressive, with sporadic relapses and remissions. Reason for this is that the immune system contains many intrinsic amplification loops that allow small numbers of antigen-specific lymphocytes to accomplish their task of eradicating complex infections. Epitope spreading is an additional reason for the persistence and progression of autoimmune disease[12].
- The clinical and pathologic manifestations of an autoimmune disease are determined by the nature of the underlying immune response. T helper 1 (T_H1) responses are associated with the destructive macrophage rich in inflammation and production of antibodies that cause tissue damage by activating complement and binding to Fc receptors.

Autoimmune disorders of the skin include psoriasis, pemphigus vulgaris, systemic sclerosis, dermatomyositis, systemic lupus erythematosus and epidermolysis bullosa.

PSORIASIS

INTRODUCTION

Psoriasis is as an autoimmune disease in which genetic and environmental factors have a significant role. The name of the disease is derived from Greek word ‘psora’ which means ‘itch’. It is a common, chronic and recurrent inflammatory disease of the skin characterized by circumscribed, erythematous, dry, scaling plaques of various sizes. The lesions are usually covered by silvery white lamellar scales. The lesions have a predilection for the scalp, nails, extensor surfaces of the limbs, umbilical region and sacrum[13].

HISTORY OF PSORIASIS

The history of psoriasis is interesting and puzzling. The biblical term ‘lepra’ was applied to various cutaneous disorders including psoriasis, vitiligo, eczema, boils and alopecia areata. The Roman sage Aurelius Cornelius Celsus is credited with the first clinical description of psoriasis. Galen was the first to use the term psoriasis and Robert Willan (1808) specifically distinguished and described it as a recognizable entity. Lepra vulgaris, described by Willan, was a variety of psoriasis. In 1841, Hebra definitively distinguished the clinical features of psoriasis from those of leprosy[14].

EPIDEMIOLOGY

Incidence & Prevalence

Psoriasis affects approximately 2 % of Americans. Prevalence ranges from 0.1% to 3% in various populations[15]. Prevalence of psoriasis in India varies from 0.44 to 2.8%. Psoriasis occurs with almost equal frequency in males and females. However, a higher prevalence in males has been noted in most Indian studies. Psoriasis can present at any age and can appear just after birth or in old age. There is a bimodal age of beginning, the first peak at 15–20 years of age and a second one at 55–60 years. The mean age of onset was about 28 years. In Indian studies have reported the highest incidence to be in the second decade or in the reproductive age group.

AETIOLOGY

Genetic epidemiology

The role of genetic factors in psoriasis is well recognized. Population genetic studies show that psoriasis is more common in the first and second degree relatives of psoriasis patients than in the common population. The risk is 2–3 times higher in monozygotic twins than in dizygotic ones. Patients with psoriasis have an greater frequency of HLA-B13, HLA-B17 & HLA-Bw16[16,17,18].

Environmental factors

Most patients experience aggravation of their skin lesions during winter. Increased humidity is usually beneficial. Sunlight may worsen psoriasis in some but improves it in many patients.

Local Factors

Psoriatic lesions tend to develop at sites of injury to the skin. The Koebner phenomenon, also known as the isomorphic response, refers to the initiation of lesions by cutaneous trauma. The trauma may be of any kind—physical, chemical, mechanical, allergic or of any other nature[19]. The Koebner phenomenon is elicited at sites of sunburn, operation wounds, vaccination and other skin lesions. It usually occurs within 7 to 14 days, but the interval may be as short as 3 days or as long as 3 weeks. Psoriasis may occur as a Koebner phenomenon at sites of bites (insects, animals), burns, drug reactions, dermatitis, lichen planus, miliaria, pressure, skin tests, vitiligo and herpes zoster. Koebner phenomenon may be mediated by trauma-induced release of neuropeptides from cutaneous sensory nerve terminals.

Pregnancy

Psoriasis may remit during pregnancy. This is due to increased IL-10 levels in the circulation which is a known type 1 immune response inhibitor. However, there may be exacerbation during the postpartum period. Rarely,

generalized pustular psoriasis may be precipitated during pregnancy probably due to raised levels of progesterone during the latter half.

Emotional Stress

Psoriasis is more 'stress sensitive' than many other skin diseases. 60% of patients explain stress is a key exacerbator for their disease. Some patients with psoriasis have an abnormal hypothalamic–adrenal axis response to acute stress. Increased beta-endorphin in psoriatic skin may affect both substance P mediated neurogenic inflammation and transmission of sensory stimuli by its confined antinociceptive effects. Stress might induce alterations in the psoriatic lesion by increasing the neuropeptide content with a concomitant decrease in activity of neuropeptide degrading enzymes, especially mast cell chymase[20].

Infections

Upper respiratory tract infections and tonsillitis, especially when caused by streptococci, may cause a flare-up of existing psoriasis or may precipitate an attack of acute guttate psoriasis[21]. This is common in children and is usually associated with an elevated antistreptolysin 'O' titre. Infections by other bacteria and viruses may also exacerbate psoriasis. Exacerbation of psoriasis may be associated with Human immunodeficiency virus (HIV) infection.

Drugs

Many drugs can precipitate or exacerbate psoriasis, particularly beta-blockers, lithium, antimalarials, imiquimod, interferons α and γ and angiotensin converting enzyme (ACE) inhibitors[22]. Treatment with beta-blockers reduces the cAMP level, accelerating epidermopoiesis and thereby exacerbating psoriasis. Psoriasiform lesions induced by such drugs are fewer scaly and less erythematous. The palms, soles and elbows are rarely involved and the eruption subsides within 2 to 6 weeks of stoppage of beta-blocker therapy[23].

Alcohol and Smoking

Psoriasis patients have high rates of excess intake of alcohol. Heavy drinking exacerbates preexisting psoriasis[24]. Two-fold increased risk of severe psoriasis is associated with smoking more than 20 cigarettes daily.

Human immunodeficiency virus (HIV) infection

Exacerbation of the initial manifestation of psoriasis has been seen in patients infected with HIV. The disease can worsen with progression of immunosuppression (possibly because of loss of regulatory T cells and increased activity of CD8 T cells), but can remit in the terminal stage [25,26].

PATHOGENETIC MECHANISMS

Epidermal proliferation

In psoriasis the increased keratinocyte proliferation is due to increase in the proliferating cell section in the basal and suprabasal layer rather than due to shortened cell cycle time. The transit from a basal keratinocyte to a desquamated cell takes 4–6 weeks in normal skin, but in psoriasis this occurs in only a few days[27].

Vascular changes

The dermal capillary loops of both involved and uninvolved skin of psoriatic patients are dilated and abnormally tortuous[28]. Neutrophils an enzymes may be migrated into the epidermis from these distorted vessels and stimulate some of the earliest dermoepidermal changes.

Molecular genetics

Genome-wide linkage analysis has identified at least nine chromosomal loci with statistically significant proof for linkage to psoriasis. *PSORS2*, a replicated locus on chromosome 17q, at which a polymorphism causing loss of binding to the RUNX1transcription factor has been identified and associated with psoriasis.

CLINICAL FINDINGS

Cutaneous Lesions:

The typical lesion of psoriasis is a well-demarcated, raised, erythematous plaque with a white scaly surface. The size of lesions can vary from pinpoint papules to plaques that involve large areas of the human body. Auspitz sign-under the scale, bleeding points become visible when the scale is removed, traumatizing the dilated capillaries below. Koebner phenomenon is the traumatic initiation of psoriasis on non lesional skin.

CLINICAL PATTERNS OF SKIN PRESENTATION

Psoriasis Vulgaris

This is the commonest type of psoriasis, being seen in 90% of patients. Red, scaly, symmetrically distributed plaques are characteristically localized to the extensor surfaces of the extremities, elbows and knees, other area involved are scalp, lumbosacral area, back and genital region.

Guttate (Eruptive) Psoriasis:

Guttate psoriasis (Latin gutta, meaning a droplet) is usually seen in children and young adults. It commonly follows an upper respiratory infection or tonsillitis especially due to β-hemolytic streptococci. Tiny, rain drop-like erythematous papules erupt abruptly and are distributed bilaterally symmetrically usually in a centripetal fashion, although they can also affect the head and limbs. The palms and soles are usually spared.

Small Plaque Psoriasis:

It resembles guttate psoriasis clinically, but can be distinguished by onset in elderly individuals, chronicity and larger lesions (typically 1 to 2 cm) that are thicker and scalier than in guttate disease.

Inverse Psoriasis:

Psoriasis lesions may present in the skin folds like axillae, neck and the genito-crural region.

Erythrodermic Psoriasis:

It is a generalized form of psoriasis characterized by total or near total erythema and superficial scaling.

Pustular Psoriasis:

In psoriasis vulgaris, the surface of a plaque is dry with silvery white, loose scales. When it is studded with tiny, superficial, sterile pustules it is called pustular psoriasis. Pustular psoriasis is broadly classified into a localized form and a generalized form. The true localized pustular psoriasis mainly affects the soles and palms. It is also known as 'pustulosis palmaris et plantaris'.

Napkin Psoriasis:

In infants and children, psoriatic lesions are sometimes localized to the napkin area. Napkin psoriasis occurs in the age group between 3 to 6 months. The lesion first starts from napkin area then progresses to trunk and limbs.

Linear Psoriasis:

Linear psoriasis is a very rare form. The psoriatic lesion presents as linear lesion most commonly on the limbs but may also be limited to a dermatome on the trunk.

LABORATORY TESTS

Markers of systemic inflammation can be increased, including C-reactive protein (CRP), α_2-macroglobulin, and erythrocyte sedimentation rate (ESR). Serum uric acid is elevated in 50 % of patients and is mainly correlated with the extent of lesions and the activity of disease. There is an increased risk of developing gouty arthritis. Serum uric acid levels usually normalize after therapy. In severe psoriasis vulgaris, generalized pustular psoriasis, and erythroderma, a negative nitrogen balance can be detected, manifested by a decrease of serum albumin.

Autoimmune diseases are managed with **immunosuppressant drugs** with better treatment outcome.

IMMUNOSUPPRESSANT DRUGS

CLASSIFICATION

1. Calcineurin inhibitors (specific T cell inhibitors)

Cyclosporine, Tacrolimus

2. m-TOR inhibitors

Sirolimus, Everolimus

3. Antiproliferative drugs (Cytotoxic drugs)

Alkylating agents - Cyclophosphamide, Chlorambucil

Folate antagonist - Methotrexate

Pyrimidine antagonist - Azathioprine

Mycophenolate mofetil (MMF)

4. Glucocorticoids

Prednisolone, Dexamethasone and others

5. Biological agents

(a) TNF α inhibitors:

Etanercept, Infliximab, Adalimumab

(b) IL-1 receptor antagonist: Anakinra

(c) IL-2 receptor antagonists:

Daclizumab (anti CD- 25 antibodies), Basiliximab

(d) Anti CD-3 antibody: Muromonab CD3

(e) Polyclonal antibodies:

Antithymocyte antibody (ATG), Rho (D) immune globulin

MANAGEMENT OF PSORIASIS

Local therapy

Coal Tar

Dithranol (anthralin)

Corticosteroids

Calcineurin inhibitors: Tacrolimus and Pimecrolimus

Vitamin D analogues: Calcitriol, calcipotriol, tacalcitol, maxacalcitol

Vitamin A analogues: Retinoids, Tazarotene

Systemic therapy

Methotrexate

6-Thioguanine

Hydroxycarbamide (hydroxyurea)

Cyclosporine

Glucocorticosteroids

Retinoids: Etretinate, Isotretinoin (13-cis-retinoic acid), Acitretin

Fumaric Acid Esters

Phototherapy

Narrowband Ultraviolet B light (290 to 320 nm)

Psoralen and UVA light (PUVA)

Excimer laser (308 nm)

Biological therapies: Etanercept, infliximab, adalimumab, ustekinumab.

Miscellaneous therapies

Sulfasalazine

Azathioprine

Mycophenolate mofetil

Cytokines

Protein kinase C inhibitor

Zidovudine (azidothymidine, AZT)

Somatostatin

Liarozole

Gluten-free diet

Photodynamic therapy

Lasers

COAL TAR

Tar is the dry distillation product of organic matter heated in the absence of oxygen.

Mechanism of action:

It depresses epidermal DNA synthesis, reducing mitotic activity in the basal layers in the epidermis and has anti-inflammatory activity[29].

Dosage:

2 - 5% of coal tar is applied daily in combination with tar bath and Ultra violet light can be used as a in-patient treatment.

Adverse effects:

Primary irritation, allergic contact dermatitis, folliculitis, carcinogenicity

Contraindications

Erythrodermic or generalized pustular psoriasis, pre-existing folliculitis

Severe acne

DITHRANOL (ANTHRALIN)

It is a synthetic derivative of anthracene[30].

Mechanism of action:

Antiproliferative activity on human keratinocytes with potent anti-inflammatory effects.

Indications:

Chronic plaque psoriasis- resistant to other therapies

Dosage:

The initial concentration is 0.05 or 0.1%, up to 4% used. The dose cautiously increased to prevent irritation of the normal or psoriatic skin.

Adverse Effects:

Irritation, burning, contact dermatitis, staining

CORTICOSTEROIDS

Introduction

In 1951 Sulzberger and associates described the use of cortisone and Adreno corticotrophic hormone (ACTH) for treatment of inflammatory dermatoses. In 1961 Reichling and Kligman suggested alternate day corticosteroids use.

Structure

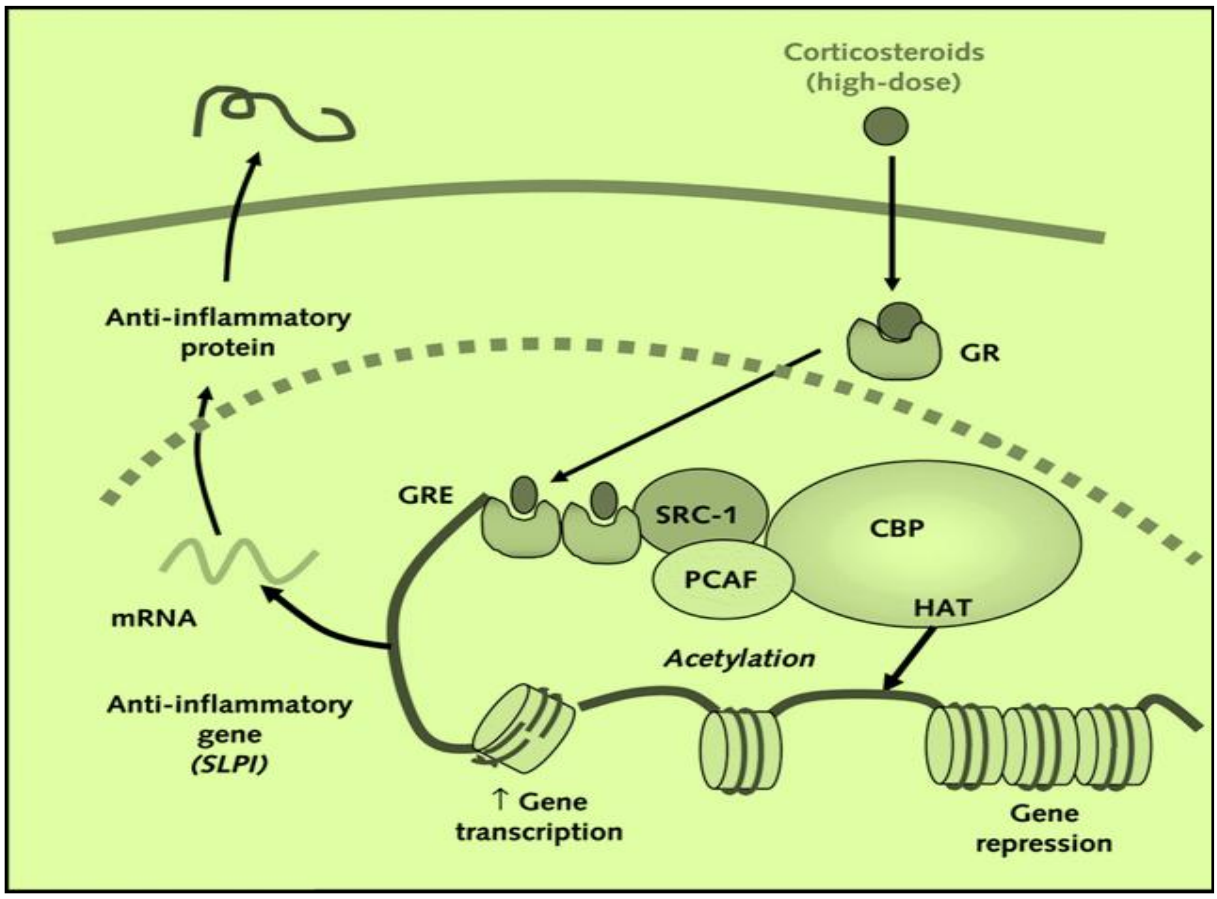
The basic structure of all corticosteroids consists of three hexane rings and one pentane ring. The ring structure is known as cyclopentanoperhydrophenanthrene nucleus[31].

Mechanism of action

Anti-Inflammatory and Immunosuppressive Actions (Figure 2)

FIGURE 2

MECHANISM OF ACTION OF CORTICOSTOIDS



Corticosteroids penetrate cells and bind to a high affinity cytoplasmic receptor protein. A structural change occurs in the steroid receptor complex that allows its migration into nucleus and binding to glucocorticoid response elements (GRE) on the chromatin that leads to transcription of specific m-RNA and regulation of protein synthesis. In addition to binding to GREs,

the ligand-bound receptor also forms complexes with and influences the function of other transcription factors, such as activator protein-1(AP-1) and nuclear factor kappa-B (NF-κB), which act on non-GRE containing promoters, to contribute to the regulation of transcription of their responsive genes. These transcription factors have broad actions on the regulation of growth factors, proinflammatory cytokines and to a great extent mediate the anti-growth, anti-inflammatory, and immunosuppressive effects of glucocorticoids[32].

Glucocorticoids cause greater suppression of cell mediated immunity in which T cells are primarily involved, e.g. delayed hypersensitivity and graft rejection. This is the basis of their use autoimmune diseases and organ transplantation. Factors involved may be inhibition of IL-1 release from macrophage, inhibition of IL-2 formation and action.

Pharmacokinetics

Absorption and distribution

Exogenous corticosteroids are absorbed in the upper intestine. Food delays the absorption. Peak plasma levels are reached 30-100 minutes after the drug is taken. 80-90% of cortisol is bound to corticosteroid-binding globulin (CBG). Corticosteroids are widely distributed to most body tissues.

Metebolism and excretion

11 β hydroxyl-steroid dehydrogenase in the liver is necessary to convert cortisone to cortisol (hydrocortisone) and to convert prednisone to

prednisolone. Only cortisol and prednisolone are biologically active. Severe liver disease may impair this conversion. The corticosteroids are metabolized primarily by hepatic microsomal enzymes. Metabolites are further conjugated with glucuronic acid or sulfate and excreted in urine.

Clinical uses

Dermatologic uses

Psoriasis

Topical corticosteroids indications

In mild to moderate psoriasis – it used as first-line treatment. Diluted topical steroid used in the treatment of unstable, erythrodermic and generalized pustular psoriasis[33].

Dosage:

Applied to affected areas twice daily for 2-4 weeks and then intermittently (weekends). 0.05% clobetasol propionate, 0.05% betamethasone dipropionate, fluticasone propionate ointments are used.

Systemic glucocorticosteroids

The fluorinated forms – triamcinolone and betamethasone are highly effective for psoriasis treatment than prednisolone. These drugs should not be used in the routine treatment of psoriasis.

Indications:

1) Persistent, uncontrollable erythroderma causing metabolic complication

2) Fulminating generalized pustular psoriasis

3) Patients with concomitant psoriatic arthritis

4) If other drugs are contraindicated or ineffective

Bullous dermatoses

Pemphigus vulgaris

Bullous pemphigoid

Cicatrical pemphigoid

Epidermolysis bullosa

Linear Immunoglobulin A (IgA) bullous dermatoses

Stevon Johnson syndrome / Toxic epidermo necrolysis (TEN)

Autoimmune connective tissue diseases

Systemic lupus erythematosus

Dermatomyositis

Systemic sclerosis

Vasculitis

Neutrophilic dermatoses

Pyoderma gangrenosum

Behcet's disease / aphthous ulcers

Sweet syndrome

Dermatitis

Contact dermatitis

Atopic dermatitis

Lichen planus

Other dermatoses

Sarcoidosis, severe urticaria

Pulse intravenous methylprednisolone

Pyoderma gangrenosum

Sweet syndrome

Pemphigus vulgaris

Bullous pemphigoid

Other uses

Replacement Therapy

Acute Adrenal Insufficiency, Chronic Adrenal Insufficiency, Congenital Adrenal Hyperplasia

Non endocrine uses

Rheumatic Disorders, nephrotic syndrome, allergic disorder, bronchial asthma, ocular diseases, inflammatory bowel disease (chronic ulcerative colitis and Crohn's disease), hepatic diseases, acute lymphocytic leukaemia, lymphomas, cerebral oedema, sarcoidosis, thrombocytopenia, haemolytic anemia with a positive Coombs test, organ transplantation and spinal cord injury.

Contraindications

Absolute

Systemic fungal infection, Herpes simplex keratitis, Hypersensitivity

Relative

Cardiovascular: Hypertension (HT), congestive cardiac failure (CHF)

Central nervous system: Prior psychosis, severe depression

Gastro intestinal tract (GIT): Peptic ulcer, recent anastamosis

Infections: Active Tuberculosis (TB)

Diabetes mellitus (DM)

Osteoporosis

Cataract, glaucoma

Pregnancy (category – C)

Adverse effects

Hypothalamo pituitary adrenal (HPA) axis: Steroid withdrawl syndrome, addisonian crisis

Metabolic side effects

Glucocorticoid effects: Hyperglycemia, increased appetite & weight

Mineralocorticoid effects

Hypertension, congestive cardiac failure, hypokalemia

Lipid effects: Hypertriglyceridemia, cushingoid changes

Bone: Osteoporosis, osteonecrosis, hypocalcaemia

Gastrointestinal tract: Peptic ulcer disease, bowel perforation, fatty liver, oesophageal changes, nausea, vomiting.

Psychiatric: Psychosis, depression

Central nervous system (CNS): Pseudotumor cerebri, peripheral neuropathy

Infections: Tuberculosis reactivation, fungal infection

Muscular: Myopathy

Paediatric: Growth impairment

Pregnancy risk: Cleft lip, cleft palate

Pulse therapy: Electrolyte shifts, cardiac arrhythmias, seizures

Cutaneous: Delayed wound healing, striae, atrophy, telangiectasias, purpura, hirsutism

Drug interactions

Ketoconozole, erythromycin, estrogen, aminoglutethamide, phenytoin, phenobarbitone, rifampicin, diuretics, digoxin, insulin, salicylates, anticoagulants.

Monitoring guidelines

Baseline examination of blood pressure, weight, height should be measured and ophthalmic examination for cataract. TB screening-tuberculin skin test, chest x ray, fasting glucose and triglycerides, potassium level should be monitored.

Follow up examination of blood pressure, weight, height should be taken for monthly once for 3 months and ophthalmic examination to be done for once in every 6 months. Fasting blood sugar, triglycerides, and potassium level should be monitored for once in 3 months.

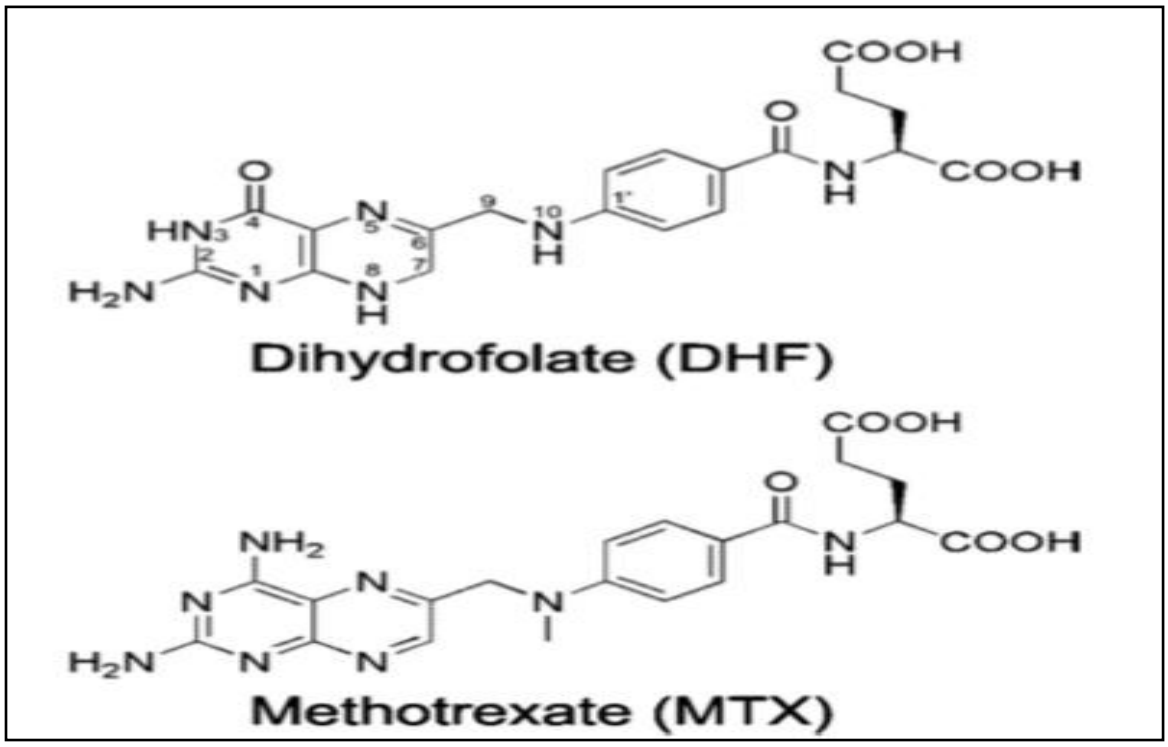
METHOTREXATE

Structure

4-amino-N^{10} methyl pteroylglutamic acid (Methotrexate) is a potent competitive antagonist of dihydrofolate reductase enzyme[34]. It is a structural analogue of folic acid (Figure 3).

FIGURE 3

CHEMICAL STRUCTURE OF METHOTREXATE



Mechanism of action:

DNA Synthesis effects:

Methotrexate reversibly and competitively binds to dihydrofolate reductase within 1 hour with an greater affinity than folic acid.

Dihydrofolate to tetrahydrofolate conversion is prevented by methotrexate. Tetrahydrofolate is essential for synthesis of thymidylate and purine nucleotide required for Deoxy ribonucleic acid (DNA) and ribonucleic acid (RNA) synthesis. Incomplete reversible competitive inhibitions of thymidylate synthetase also occur. The effect of methotrexate is inhibition of cell division specific for S phase of normal cell cycle in DNA synthesis. The inhibition of dihydrofolate reductase is bypassed by Leucovorin calcium (citrovorum factor, Folinic acid, N^5 formyl tetrahydrofolate) or thymidine.

T cell effects:

Mechanism of action of methotrexate in psoriasis was due to suppression of hyperproliferation of keratinocytes. The effect of methotrexate on the proliferation of lymphoid cell is 100 times higher than its effect on keratinocytes. Methotrexate acts via an immunosuppressive mechanism. Depressions of cutaneous lymphocyte - associated antigen positive T cells and endothelial E – selectin in methotrexate treated psoriatic patients have been demonstrated by Sigmundsdottir and colleagues.

Immunosuppressive effects:

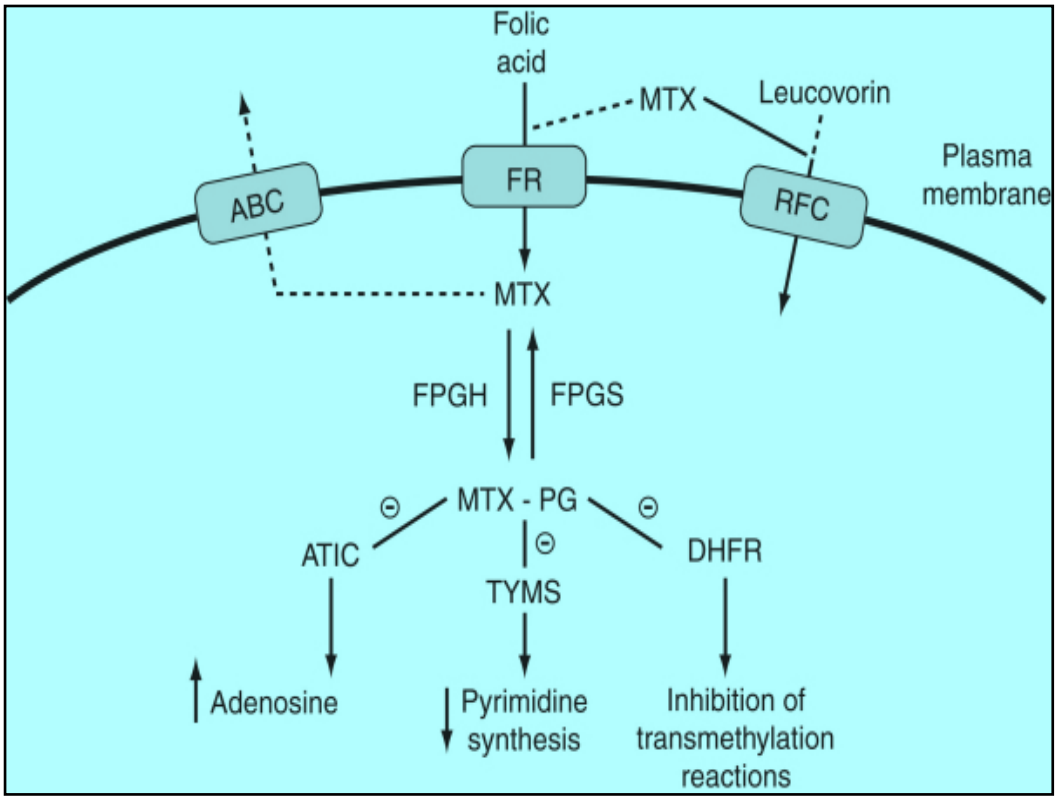
Methotrexate is an Immunosuppressive agent. The effect is due to inhibition of DNA production in immunologically competent cells. Primary and secondary antibody response can be suppressed by methotrexate[35].

Anti-inflammatory effects:

These effects mediated by adenosine predominantly. This augmented adenosine production is the effect of complex amino imidazole carboxamide ribonucleotide (AICAR) transformylase and ecto 5'nucleotidase[36] (Figure 4).

FIGURE 4

MECHANISM OF ACTION OF METHOTREXATE



Folic acid effects on Methotrexate therapy:

Folic acid is used to inhibit methotrexate induced gastrointestinal side effects like mucosites, nausea and reduction of pancytopenia risk. Many studies in rheumatology literature suggested that folic acid administration

does not impair the efficacy of methotrexate. Folic acid (1-3 mg/day) is cheap compared to folinic acid (2.5-5mg/day). Morgan and colleagues have confirmed and demonstrated that folinic acid administration, but not folic acid, reduces the efficacy of methotrexate[37].

Pharmacokinetics

Absorption:

Methotrexate can be administered orally, intravenously, intramuscularly and subcutaneously. Rapidly absorbed from gastrointestinal tract, attain peak level after 1 hour of ingestion. Oral methotrexate absorption is incomplete and variable. Food intake decreases the bioavailability in children. In adult the drug is unaffected by food intake.

Distribution:

Drug is well distributed throughout the body expect in the brain because of poor penetration through blood brain barrier (BBB).

Metabolism & Excretion:

50% of methotrexate is bound to plasma proteins and free fraction is the active form of drug in the plasma. Drug is metabolized intracellularly by the liver to polyglutamate forms. This metabolite is the potent inhibitor of dihydrofolate reductase enzyme. Excreted by glomerular filtration and active tubular secretion.

Clinical uses

Indications

Food and Drug Administration (FDA)-approved dermatologic indications

Psoriasis

Sezary syndrome

Off- label dermatologic uses

Proliferative dermatoses

Pityriasis rubra pilaris

Reiter's disease

Immunobullous dermatoses:

Pemphigus vulgaris

Bullous pemphigoid

Cicatrical pemphigoid

Epidermolysis bullosa acquisita

Autoimmune connective tissue diseases:

Dermatomyositis

Systemic lupus erythematosus

Systemic scleroderma

Localized scleroderma

Indications for Methotrexate therapy in psoriasis:

Erythrodermic psoriasis

Psoriatic arthritis

Pustular psoriasis: Generalized or debilitating localized disease

Extensive severe plaque psoriasis

Lack of response to phototherapy or systemic retinoids

Other uses:

Graft-versus-host disease, rheumatoid arthritis, acute lymphoblastic leukaemia (ALL) in children, choriocarcinoma, burkitt's and other non-Hodgkin's lymphomas, carcinomas of the breast, head and neck, ovary, and bladder.

Efficacy:

Initial response occurs within 1-4 weeks with methotrexate treated psoriatic patients. Full therapeutic benefit occurs within 2-3 months.

Dosage:

15-20 mg weekly will be adequate for satisfactory response.

Contraindications:

Absolute:

Pregnancy- Category X, Lactation

Relative:

Excessive alcohol intake

Renal failure patients

Metabolic- Diabetes mellitus, obesity

Hepatic disease- Active hepatitis, cirrhosis, abnormal liver function test.

Severe hematologic abnormalities

Active infectious diseases

Immunodeficiency syndrome: Hereditary or acquired

Adverse effects:

Gastrointestinal effects:

Nausea, anorexia are common adverse reaction. Diarrhoea, vomiting, ulcerative stomatitis are less commonly seen. Methotrexate therapy can be stopped if ulcerative stomatitis or diarrhoea develops. Studies showed folic acid reduces GI toxicity without reducing the efficacy.

Hepatotoxicity:

Patients treated with long-term methotrexate are prone to develop hepatotoxicity[38]. Risk of hepatic damage is low for a cumulative dosage of 1.5 g. If the cumulative dose at or above 4 g is risky for liver fibrosis and cirrhosis. Non-invasive test to diagnose methotrexate induced hepatotoxicity are hepatic ultrasound. Amino-terminous of type III procollagen peptide is a serum test used to assess ongoing hepatic fibrosis. Liver biopsy is the gold standard test for accurate diagnosis of methotrexate induced hepatic fibrosis and cirrhosis.

Pulmonary toxicity:

Acute pneumonitis can occur. This pulmonary toxicity is idiopathic, can occur with small doses of methotrexate, and can be life-threatening if methotrexate is not stopped. Chest x ray shows pulmonary fibrosis.

Hematologic effects:

Pancytopenia risk is reduced by routine folic acid supplementation. It is more commonly due to drug interactions with methotrexate, such as trimethoprim /sulfamethaxazole combinations and non-steroidal anti-inflammatory drugs.

Renal effects:

Renal toxicity secondary to methotrexate precipitation in the renal tubules. It occurs with high doses of 50 to 250 mg/m^2 intravenously used in chemotherapy for malignant diseases. This toxicity is not likely to occurr with low-dose therapy for psoriasis or other dermatologic conditions.

Malignancy induction:

Lymphoma has been rarely reported in patients with psoriasis.

Reproductive effects:

Methotrexate is a potent terratogen and abortifacient. Methotrexate is category X drug in pregnancy. Women of childbearing potential who take methotrexate should adopt reliable birth control measures. Reversible oligospermia can occur in men.

Other adverse effects

Anaphylaxis, mild alopecia, headache, fatigue, and dizziness. Potent phototoxic, acral erythema, epidermal necrosis, cutaneous ulceration, vasculitis, osteopathy, stress fractures etc.

Morgan and colleagues suggested that with long term methotrexate therapy, homocysteine level increases and can be lowered by folic acid therapy. This leads to cardiovascular diseases[39].

Drug interactions:

Drugs that increases methotrexate serum levels by displacement from plasma proteins are phenytoin, tetracycline, doxycycline, phenothiazines. These drugs may increase methotrexate serum levels by decreasing renal excretion. Sulfamethoxazole, salicylates and NSAIDS may displace the methotrexate from plasma proteins and increases the serum methotrexate level. Methotrexate may increases the serum level of theophylline and decreases the serum level of digoxin. Drugs that inhibit folate metabolic pathways and increases hematologic toxicity are trimethoprim, sulphonamides and dapsone. Drugs that synergistically increase hepatotoxicity are systemic retinoids, alcohol.

Methotrexate monitoring guidelines:

Baseline examination:

Careful history and physical examination to identify the high risk patients. Concomitant medications may interact with methotrexate.

Laboratory investigations:

Complete hemogram, liver function tests (LFT), serological test for hepatitis B & C, blood urea, serum creatinine and HIV testing for patients at risk for AIDS should be monitored.

Follow-up investigations:

Laboratory: Complete hemogram and liver function tests 5-6 days after first dose followed by every 1-2 weeks for 2-4 weeks followed by every 3-4 months. Renal function tests once in 6 months should be monitored.

Liver biopsy:

Low risk patients-After every 1.5-2 g total dose

Higher risk patients- After every 1 g total dose

Every 6 months for patients with grade III A liver biopsy changes

WBC count is less than 3500/ mm^3, platelet count is less than 100,000/mm^3, elevated liver transaminase levels are the indications to decrease the dosage of methotrexate. Gradual dose escalation is to be done without noticeable toxicity. First start with low dose of 5-10 mg /week then increased to 10-15mg / week.

6-THIOGUANINE

Mechanism of action

Purine analogue that interferes with purine biosynthesis, thereby inducing cell cycle arrest and apoptosis[40].

Dosage: Initial dose is 80 mg twice weekly, gradually increase 20-mg for each 2-4 weeks. Maximum dose, 160 mg three times weekly.

Adverse effects:

Bone marrow depression; GIT manifestations - nausea and diarrhoea, hepatic dysfunction, hepato venous-occlusive disease.

Contraindications

Absolute:

Patients with inherited deficiency of thiopurine methyltransferase enzyme, liver toxicity, pregnancy (category: D)

HYDROXYCARBAMIDE (HYDROXYUREA)

Mechanism of action

Inhibits ribonucleotide diphosphate reductase, which converts ribonucleotides to deoxyribonucleotides, thus selectively inhibiting DNA synthesis in proliferating cells[41].

Indications

Extensive chronic plaque psoriasis

Dosage

Initial dose is 500 mg daily, can be increased up to 1.0-1.5 g.

Adverse effects

Bone marrow depression, macrocytosis, teratogenicity and mutagenicity.

Dermatologic side effects are lichen planus-like eruptions, exacerbation of post-irradiation erythema, leg ulcers, and dermatomyositis changes.

Monitoring

Baseline: Complete blood count, blood sugar, lipid profile, liver function tests (LFT) should be done. Repeat the test weekly for 1 month, followed by every 2-4 weeks for at least 3 months. Then repeat tests every 3 months. Stop the drug if WBC $< 2.5 \times 10^9$/L, platelet count is $< 100 \times 10^9$/L or if there is severe anaemia.

Contraindications

Absolute:

Bone marrow depression (leukopenia, thrombocytopenia, anaemia),

Pregnancy (category: D), lactating women.

Relative: Abnormal renal functions

FUMARIC ACID ESTERS

Mechanism of action

Interferes with intracellular redox regulation, inhibiting nuclear factor- kappa B (NF-κB) translocation. Skews the T-cell response towards a Th2-like pattern[42].

Indications: Moderate to severe psoriasis

Adverse effects: GIT symptoms- diarrhoea, flushing, headache, lymphopenia, acute renal failure

Contraindications

Absolute:

Chronic disease of the gastro intestinal tract or renal disease

Pregnancy (category: D), lactating women, malignancy

Cyclosporine

Cyclosporine is derived from the fungus Tolypocladium inflatum gams.

Mechanism of action

Binds cyclophilin, and the resulting complex blocks calcineurin, reducing the effect of the NF-AT in T cells. Results in inhibition of interleukin 2 and other cytokines[43].

Dosage: High-dose approach: start with 5 mg/kg/day then reduce gradually.

Low-dose approach: start with 2.5 mg/kg/day, then increased every 2-4 weeks up to 5 mg/kg/day.

Adverse effects:

Nephrotoxicity, hypertension, immunosuppression and increased risk of malignancy

Monitoring

Blood pressure, baseline complete blood counts, complete metabolic profile, magnesium, uric acid, lipid profile should be monitored. Repeat tests every 2-4 week, then every month along with blood pressure.

Contraindications

Absolute: Uncontrolled hypertension, abnormal renal function, malignancy, pregnancy (category: C).

TOPICAL CALCINEURIN INHIBITORS: Tacrolimus and Pimecrolimus

Mechanism of action:

Bind to FK506-binding protein (FKBP) and inhibit calcineurin, decreasing the activation of the transcription factor, NF-AT, with resultant decrease in cytokine transcription, including interleukin 2 (IL-2).

Indications:

Facial and flexural psoriasis

Chronic plaque psoriasis

Adverse effects:

Burning sensation

Lymphoma

Contraindicated in pregnancy (category: C)

Vitamin D and its Analogues

1). Naturally occurring – Calcitriol, active metabolite of vitamin D (1, 25-dihydroxyvitamin D3)

2). Three synthetic analogues-

a. Calcipotriol

b. 1, 24 -dihydroxyvitamin D3 (tacalcitol) and

c. 1, 25 -dihydroxyvitamin D3 (maxacalcitol)

Mechanism of action:

It reduces keratinocytes proliferation and enhances differentiation within the skin lesions of the psoriasis patients. These effects are mediated through vitamin D receptors situated in the nucleus of keratinocytes. It also inhibits T cell proliferation in response to IL-1 and decreases T cell permeation and keratinocyte intracellular adhesion molecule–1 (ICAM-1) appearance in treated plaques, thus exerting an immunomodulatory effect[44].

Indications:

Chronic plaque psoriasis

Dosage:

Calcipotriene, 0.005% - topical application for twice daily

Adverse effects:

Irritation, hypercalcemia

Contraindications:

Hypercalcemia, vitamin D toxicity

Pregnancy (category: C)

VITAMIN A ANALOGUES

Retinoids: Topical therapy

Tazarotene: Synthetic third-generation retinoid

Mechanism of action:

Metabolized to tazarotenic acid - active metabolite, this binds to the retinoic acid receptors. Normalizes epidermal differentiation, exhibits a potent antiproliferative effect and decreases epidermal proliferation.

Indications:

Treatment of chronic plaque psoriasis

Dosage: Topical application of 0.05 or 0.1% gel daily (night) for 3months

Adverse effects: Local irritation

Contra indications:

Pregnancy (category: X)

Hypersensitivity to tazarotene

Systemic Retinoids

Etretinate

In 1986, etretinate was accepted for the psoriasis management.

Dosage & Indications: 1 mg/kg daily, used for the treatment of psoriasis vulgaris, erythrodermic and pustular psoriasis has been demonstrated.

Isotretinoin (13-cis-retinoic acid)

Indications:

Pustular psoriasis of generalized form

Acitretin

Acitretin is the single oral retinoid commonly used for the management of psoriasis. It is a second-generation monoaromatic retinoid, active metabolite of etretinate, the trimethyl-methoxyphenyl analogue of retinoic acid-ethyl-ester. It is less lipophilic than etretinate with a half-life of 50 to 60 hours but equally effective.

Mechanism of action

It acts by binding to retinoic acid receptors and leads to improvement by normalizing keratinization and proliferation of the epidermis.

Dosage: Initiate at 25-50 mg daily

Adverse effects

Liver damage, lipid abnormalities, fetal abnormalities or death, hair loss, mucocutaneous toxicity, hyperostosis.

Contraindications

Absolute

Pregnancy during or within 3 years after termination of acitretin (category: X) Lactation

Monitoring

Baseline liver function tests (LFTs), complete hemogram, lipid profile, pregnancy test should be done. Repeat liver function tests (LFTs), complete hemogram; lipid profile should be monitored weekly for 1 month followed by monthly once. Pregnancy test every month for females

PHOTOTHERAPY:

Mechanism of action:

It acts by depletion of T cells selectively in the epidermis. The mechanism of depletion due to apoptosis and is accompanied by a move from a Th1 immune response toward a Th2 response in the lesional skin.

Narrowband Ultraviolet B Light (290 to 320 nm)

Dosage:

The first therapeutic Ultraviolet B (UVB) dose was 50% to 75% of the minimal erythema dose (MED). Treatments given for 2 to 5 times / week. As maximum UVB erythema appears within 24 hours of exposure, dose can be increased at every successive treatment.

Adverse effects:

Photodamage

Polymorphic light eruption

Increased risk of skin aging

Skin cancers

Contraindications

Absolute: Photosensitivity disorders

Relative:

Photosensitizing medications

Melanoma and nonmelanoma skin cancers

Psoralen and UVA Light (PUVA)

Topical psoralens followed by long-wave Ultraviolet A (UVA) radiation

Dosage:

Start with dose 0.5-2.0 J/cm^2, depending on skin type or minimal phototoxic dose. Treat twice weekly with increments of 40% per week until erythema appears. No further increments once 15 J/cm^2 is reached.

Efficacy:

It induces remission in 70-90% of patients and less convenient but more effective than Narrowband ultraviolet B (NB-UVB).

Indications:

Pustular psoriasis of generalized form, erythrodermic psoriasis, palmoplantar psoriasis, nail psoriasis

Adverse effects

Photo damage, premature skin aging, increased risk of melanoma,

Nonmelanoma skin cancers

Ocular damage- Eye protection required with oral psoralens

Contraindications

Absolute: Light-sensitizing disorder, melanoma, lactation

Relative: Age less than ten years, pregnancy, photosensitizing medications, nonmelanoma skin cancers, severe organ dysfunction

Excimer laser (308 nm)

Dosage

Up to 6 minimal erythema dose (MED), twice weekly.

Adverse effects

Erythema, blisters, hyperpigmentation, erosions

BIOLOGICAL THERAPIES

The British Association of Dermatologists has guidelines for usage of these drugs, and their use should be restricted to (i) patients with severe illness defined by a psoriasis area severity index (PASI) score of 10 or greater (or a body surface area (BSA) of 10% or more where PASI is not applicable) and dermatology life quality index (DLQI) of greater than 10 and (ii) who have failed to respond or contraindication or intolerant to other systemic therapies such as cyclosporine and methotrexate[45].

Five biological agents approved for the treatment of psoriasis vulgaris are

- Etanercept, a fully human soluble p75 TNF-α receptor fusion protein,
- Infliximab, a human murine chimeric monoclonal antibody to TNF-α,
- Adalimumab, a fully human recombinant antibody to TNF-α,
- Ustekinumab, a fully human recombinant antibody to the p40 component of IL-12/IL-23 and
- Alefacept, a fusion protein of lymphocyte function associated antigen-3 and Ig G that inhibits T-cell activation.

MISCELLANEOUS THERAPIES

Sulfasalazine

It is anti-inflammatory agent and used as the alternative systemic therapy for psoriasis.

Mycophenolate mofetil

Mycophenolic acid is the active metabolite. It acts by inhibiting inosine monophosphate dehydrogenase vital for de novo purine synthesis and leads to blockade of T and B cell proliferation. It is effective as monotherapy for psoriasis.

Cytokines

The psoriatic plaques contain a dominance of Th1 cytokines such as IL-2, IL-12 and IFN-γ. IL-10 seems to neutralize the Th1 and recover the psoriatic lesions.

Protein kinase C inhibitor

The orally administered novel protein kinase C inhibitor, AEB071, demonstrated efficacy in moderate-severe plaque psoriasis. It was well tolerated and its mechanism of action is believed to reside in inhibition of T-cell activation.

Zidovudine (azidothymidine, AZT)

Indicated in retinoid-resistant AIDS-associated psoriasis and when contraindication to methotrexate, cyclosporine and PUVA therapy.

Somatostatin

In recalcitrant psoriasis intravenous somatostatin has been found to be beneficial.

Liarozole

It is a retinoic acid 4-hydroxylase inhibitor. Trials show that liarozole is useful for chronic plaque psoriasis.

Lasers

Lasers can be used in the management of recalcitrant psoriasis

AUTOIMMUNE BULLOUS DISEASES

PEMPHIGUS

DEFINITION:

Pemphigus refers to a set of chronic autoimmune blistering diseases of skin and mucous membranes that are characterized histologically by intraepidermal blister formation due to acantholysis (i.e., separation of epidermal cells from each other) and immunopathologically by the presence of bound and circulating immunoglobulin G (IgG) focussed against the intercellular adhesion structures of the epithelial cells. Pemphigus derived from the Greek ‘pemphix’ to describe blister or bubble.

CLASSIFICATION OF PEMPHIGUS

Pemphigus is divided into two major subtypes depending on the location of the blister in the epidermis:

- Superficial - a) Pemphigus foliaceus (PF)
  b) Pemphigus erythematosus
  c) Endemic pemphigus foliaceus (Brazilian PF)
- Deeper - a) Pemphigus vulgaris (PV)
  b) Pemphigus vegetans

PEMPHIGUS VULGARIS

EPIDEMIOLOGY

Pemphigus is an uncommon disease; the incidence varies from 0.5 to 3.2 cases per 100,000 populations per year. The disorder has been reported to occur from the age of 3 to 89 years, though it is mainly a disease of middle age. Some Indian studies have found men more frequently affected than women, though both sexes are generally believed to be equally affected[46]. Unlike in western countries, pemphigus vulgaris in India is seen in younger individuals[47]; Fourth and fifth decades is the commonest onset of age and the disease may occur in children also. It has been our experience that when exacerbations occur, they frequently come in winter.

AETIOLOGY

Genetic Determinants

Susceptibility to pemphigus vulgaris has been linked to HLADRB1* 0402, 1401/04 and DQB1*0503, suggesting that genetic factors are involved in the development of the disease, probably by regulating the autoimmune responses to Dsg3 and Dsg1 [48].

Environmental Factors

Sunlight exposure may worsen endemic pemphigus foliaceus and pemphigus vulgaris.

Immunological Factors

Pemphigus is an autoimmune disease where the autoantibodies are directed against antigens located in the epidermis.

Thymoma or Myasthenia Gravis

Lupus erythematosus

Lymphoproliferative diseases - Castleman's tumours

Drug-Induced Pemphigus

The causes of drug-induced pemphigus can be divided into two groups according to their chemical structure:

1. Thiol drugs or SH drugs, whose molecules contain a sulfhydryl or thiol group in their chemical structure e.g. penicllamine, captopril, pyritinol, piroxicam and thiopronine. D-Penicillamine is the commonest causative

drug. Up to 7% of patients treated with D-penicillamine for more than 6 months acquire pemphigus.

2. Non-thiol drugs e.g. penicillin, ampicillin, amoxicillin, cefadroxil, rifampicin, propranolol, phenytoin and phenobarbitone[49].

CLINICAL FEATURES

The most common subtype, pemphigus vulgaris (PV) manifested with oral blisters and erosions seen in 50%–70% of patients. Skin lesions appear after a period of several weeks to a year or more. The cutaneous lesions are vesicles and bullae on apparently normal or erythematous skin. They may be localized or generalized. The sites largely involved are scalp, face, axillae and the oral cavity, areas where the PV antigen is maximally expressed. Blisters may also appear on the palms and soles. The bullae are initially tense and clear but become flaccid and turbid in two to three days. Nikolsky's sign, which is separation of epidermal layers on application of lateral pressure to normal-appearing skin is demonstrable in most cases. It is characteristic but not diagnostic of pemphigus. It may also be present in unrelated conditions like toxic epidermal necrolysis.

DIAGNOSIS

Histopathology

An early vesicle or bulla should be selected for biopsy. The earliest changes are intercellular edema and disappearance of the intercellular bridges in the lowermost epidermis. Loss of coherence between epidermal

cells (acantholysis) leads to the formation of clefts and then of bullae in the suprabasal zone. Acantholytic cells are present in the bulla cavity.

Direct Immunofluorescence

Direct immunofluorescence (DIF) is a one-step procedure for the detection of in vivo bound antibody, complement components and fibrinogen in the patient's skin.

Indirect Immunofluorescence

Indirect immunofluorescence (IIF) is a two-stage procedure for in vitro demonstration of circulating antibodies in the patient's serum. The serum is added to a substrate, resulting in fixation of circulating antibodies to the antigen in the substrate. The next step consists of the application of fluorescein-labeled antihuman gamma globulin serum to the substrate. When the substrate is viewed through a fluorescence microscope intercellular fluorescence is seen.

ELISA

Enzyme-linked immunosorbent assays (ELISA) that detect IgG autoantibodies to Dsg1 and Dsg3 have been developed. These assays are highly sensitive and specific for the diagnosis of both PF and PV and simpler and more quantifiable than immunofluorescence.

TREATMENT OF PEMPHIGUS VULGARIS

Before initiating specific treatment measures, it is important to assess the general condition and extent and severity of the disease. Particular attention should be paid to general nursing care, nutrition and control of secondary infection. There may be loss of fluid and electrolytes from denuded areas, especially in severe and extensive disease and efforts should be made to maintain adequate fluid and electrolyte balance. Adequate nutrition may require oral supplementation with proteins and high calorie fluids. A soft, easily chewable diet is preferable in the presence of oral lesions. Cleaning of teeth and maintenance of proper oral hygiene is important in the presence of oral disease.

Topical Therapy

- Patients with painful oral ulcers can be encouraged to mix hydrogen peroxide with warm water (1:1) and swish and spit out 4 times a day to remove necrotic tissue. After each meal, gargling of this mixture is carried out and a corticosteroid gel can be applied.
- Triamcinolone acetonide oral paste can be applied to a small piece of gauze and kept on the affected area for 10 minutes 3 times daily.
- Intralesional triamcinolone acetonide (2.5–5 mg/ml) is helpful for intractable oral ulcers.

- Oral candidiasis should be treated with clotrimazole troches four times a day or with oral fluconazole 150–200 mg 1–7 times per week.
- Topical tacrolimus has been recently found to be effective in healing such localized and refractory erosions[50].

SYSTEMIC THERAPY

SYSTEMIC CORTICOSTEROIDS

DEXAMETHASONE - CYCLOPHOSPHAMIDE PULSE THERAPY

Definition

It refers to administration of large supra pharmacologic doses of drugs intermittently to enhance the therapeutic effects as well as to reduce the adverse effects.

The aim of pulse therapy is to set quicker and stronger efficacy and to decrease the long term need for corticosteroids and other immunosuppressant drugs, thereby reducing adverse effects associated with long term use of these agents. In an attempt to induce prolonged remissions, Paricha et al pioneered and persevered to evolve a curative treatment for pemphigus and investigated the efficacy of dexamethasone - cyclophosphamide (DCP) pulse therapy in this disease. DCP therapy involves the intravenous administration of 100 mg dexamethasone with cyclophosphamide 500 mg in 5% dextrose 500 ml over 1-2 hour on day 1, followed by daily administration of 100 mg of dexamethasone for the next 2

days. This pulse therapy is repeated every 4 weeks. On the remaining days 50 mg of cyclophosphamide is administered orally every day[51].

Treatment is divided into four phases:

In the **first phase**, this lasts till remission is achieved (6 months - 1 year). Erosions dry up almost completely within 3 days after a pulse but new lesions can appear. Recurrences progressively become milder with each pulse and next phase commences when no new lesion appear.

In the **second phase**, the period of remission while on therapy monthly DCPs and oral cyclophosphamide are continued every 28 days cycles for 9 months despite the absence of clinical lesion.

Phase 3 – If the patient remains in remission, the pulses are terminated, cyclophosphamide 50 mg per day orally continued for the subsequent 9 months

Phase 4 – If there is no relapse, all the treatment is stopped and the patient is followed up for the next 10 years to look for any recurrence of the disease.

Indications

Autoimmune and dermatological diseases

Severe pemphigus, bullous pemphigoid, cicatrical pemphigoid,systemic sclerosis, systemic lupus erythematosus, dermatomyositis, scleromyxedema , pyoderma gangrenosum.

Contraindications

Pregnancy, lactation

Advantages of DCP therapy

1. Quick healing of lesions and rapid control of disease. Usually skin lesions improve within three to four days.

2. Absence of side effects of long term steroid therapy such as weight gain, diabetes, hypertension, cushingoid habitus, obesity, cararact, acne, hirsutism and osteoporosis.

3. Concomitant diseases such as diabetes, hypertension can be managed appropriately without interrupting DCP therapy.

4. Can be given to patients of all ages, doses have to be reduced to half in children less than 12 years of age.

The DCP therapy is effective and safer than the daily dose regimens in spite of the high dose used.

Adverse effects

Increased susceptibility to infections – secondary bacterial infection of the lesion, oral candidiasis, tinea infection, reactivation of dormant tuberculosis.

Irreversible amenorrhoea in women, azoospermia in men and hair loss.

Commonest immediate side effect of DCP is flushing, followed by generalized weakness and inadequate sleep syndrome. Rarely pancytopenia and septicaemia occur. Pituitary –adrenal axis suppression present in half of

those on DCP therapy. But these side effects are infrequent compared to daily doses of corticosteroids.

Failure to respond to DCP was seen in incomplete or irregular therapy (not taking the pulses exactly after completion of 4 weeks), and in those used only one drug for pulse therapy.

IMMUNOSUPPRESSIVE AGENTS

These drugs are indicated when high dose of glucocorticoids are required for disease control or contraindications to oral glucocorticoids.

AZATHIOPRINE

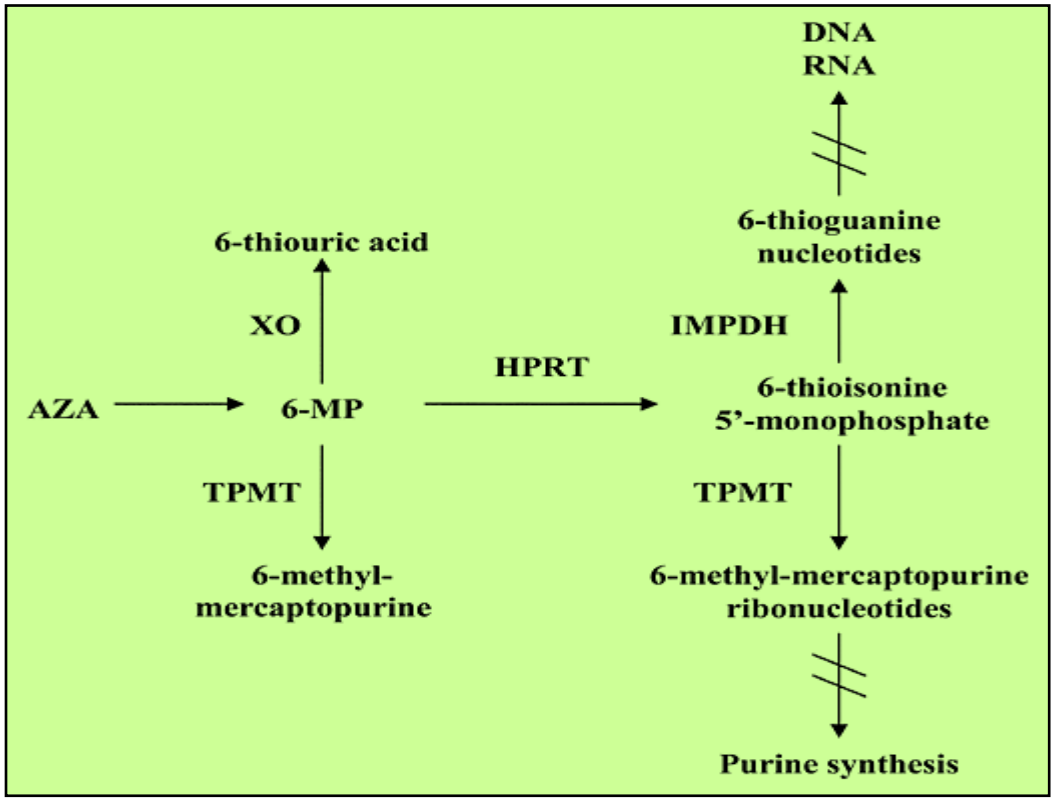
It is a first line immunosuppressive agent for treatment of pemphigus[52]. It was synthesized in 1959 from its parent drug 6-mercaptopurine.

Mechanism of action

It has immunosuppressive and anti-inflammatory effects. 6 - Thioguanine (6-TG) structurally similar to endogenous purines allows it to be integrated into DNA and RNA, arresting purine metabolism and cell division. It affects T and B cell function and antigen presenting cell function and number. It depresses T- cell mediated function and decreases antibody production by B cell[53]. This altered antibody production is importance to azathioprine treatment for immunobullous dermatoses such as pemphigus vulgaris and bullous pemphigoid (Figure 5).

FIGURE 5

MECHANISM OF ACTION OF AZATHIOPRINE



Pharmacokinetics

Absorption and distribution

It has 88% oral bioavailability, 30% plasma protein bound, does not cross blood brain barrier, but easily crosses placenta. Peak plasma level occurs 1-2 hour of drug administration. It is rapidly and extensively metabolized. 6-Thioguanine is a active metabolite which slowly accumulates in tissues and provides maximal immunosuppression at around 8-12 weeks.

Metabolism and excretion

Three pathways for azathioprine metabolism. Azathioprine is rapidly converted to 6-mercaptopurine after absorption. This conversion occurs mainly in erythrocytes. The fate of 6- mercaptopurine is determined by the following three competing pathways.

1. Anabolized to its active form, a purine analogue 6 – thioguanine by the enzyme hypoxanthine guanine phosphoribosyltransferase (HGPRT)
2. Degraded by thiopurine methyltransferase(TPMT) to inactive metabolites
3. Degraded by xanthine oxidase to inactive metabolites

Reduced activity of either of the degradative pathways will have dramatic effects clinically, because it will shift more of the 6 – mercaptopurine into the hypoxanthine guanine phosphoribosyltransferase (HGPRT) active pathway leading to excessive clinical immunosuppression, with an increased risk of myelosuppression.

Thiopurine methyltransferase polymorphism (TPMT)

TPMT activity is absent or reduced in some patients with genetic polymorphism. The enzyme function test involves measuring the TPMT in red blood cells. This functional assay system, three groups of patients has been identified[54] high activity, intermediate activity and low activity. Patients with low TPMT activity have increased accumulation of 6-TG

metabolites, which increases the risk of myelosuppression. These patients should not be treated with azathioprine. The patients with high level TPMT activity dose should be increased.

Dosage based on TPMT activity

Empiric - Up to 2-2.5mg / kg daily

Drug dosing by TPMT level

High TPMT - 15.1-26.4 U/ml – Up to 2-2.5 mg/kg daily

Medium TPMT - 6.3-15 U/ml – Up to 1.0 mg/kg daily

Low TPMT - 6.6 U/ml – Do not use azathioprine

Indications

FDA – approved indications

Organ transplantation

Severe rheumatoid arthritis

Off- label dermatologic uses

Immunobullous dermatoses

Bullous pemphigoid

Pemphigus vulgaris

Cicatrical pemphigoid

Vasculitis

Polyarteritis nodosa

Wegeners granulomatosis

Neutrophilic dermatoses

Behcet's syndrome, Pyoderma gangrenosum

Autoimmune connective tissue diseases

Systemic lupus erythematosus

Discoid lupus erythematosus

Dermatomyositis/ polymyositis

Dermatitis and papulosquamous dermatoses

Contact dermatitis

Atopic dermatitis

Lichen planus

Psoriasis

Photodermatoses

Polymorphous light eruption

Other dermatoses

Sarcoidosis

Erythema multiforme

Other uses

Severe rheumatoid arthritis, prevention of organ transplant rejection

Contraindications

Absolute: Pregnancy (Category: D), Hypersensitivity to azathioprine, active infection

Relative: Allopurinol use, prior use of alkylating agents

Adverse effects

Malignancies: Cutaneous squamous cell carcinoma, lymphoma

Myelosuppression

Neutropenia, agranulocytosis and pancytopenia - cessation of drug therapy considered if reduced blood counts occur (WBC < 3500-4000 /mm^3, Hemoglobulin < 10 g/dl, Platelets < 100000 / mm^3)

Infections

Human papilloma virus, herpes simplex, scabies

Opportunistic infections

Teratogenicity

Various congenital malformations-preaxial polydactyly, myelomeningocele, bilateral hip dislocation, bilateral talipes equinovarus.

Hypersensitivity syndrome

Cardiovascular collapse, fever, leukocytosis.

Gastrointestinal discomfort- nausea, hepatotoxicity, pancreatitis, arthralgia, myalgias, renal insufficiency, cough, pneumonitis.

Cutaneous aspects- morbilliform, purpura, erythema multiforme, urticaria, angioedema, erythema nodosum[55].

Hepatic effects

Transaminase elevations, rarely severe hepatocellular toxicity

Drug interactions

ACE inhibitors – captopril, may increase the risk of leukopenia. Allopurinol inhibits the XO pathway and co administration of allopurinol with azathioprine results in more active 6 TG production, which leads to excessive immunosuppression and increased risk of myelosuppression. Sulfasalazine inhibits TPMT enzyme activity and may potentiate azathioprine toxicity.

Azathioprine may decrease anticoagulant effect of warfarin and cyclosporine plasma level may be decreased.

Monitoring guidelines

Baseline clinical evaluation

Elicit history of prior alkylating agents and discuss the risk/ benefit profile and adverse effects with each patient. Careful physical examination and discuss birth control/ abstinence if women of child bearing age.

Laboratory

Pregnancy test (for women of child bearing potential) should be done. Complete hemogram, liver function tests, renal function test, blood sugar should be monitored. Tuberculosis to be ruled out before starting the treatment.

Special tests

TPMT assay

The follow-up

Clinical evaluation

Annual complete physical examination for lymphoma, squamous cell carcinoma.

Laboratory

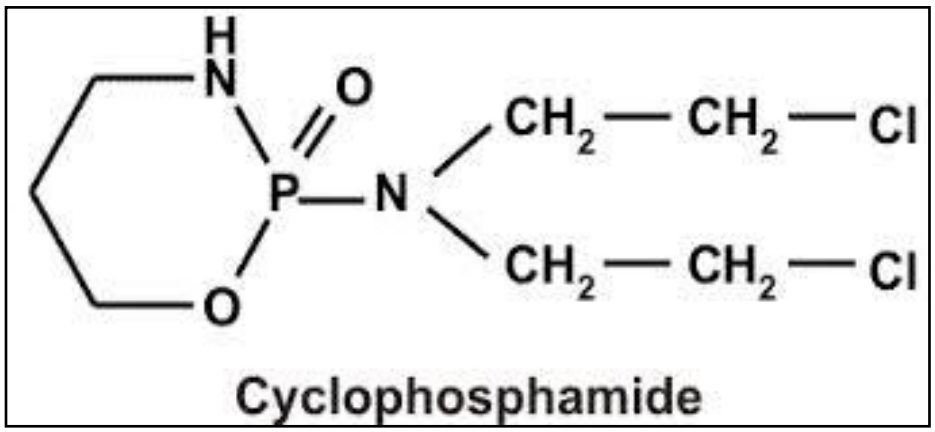
Complete hemogram and liver function test is monitored for 15 days once for 2 months, followed by once in every 3 months.

CYCLOPHOSPHAMIDE

Introduction: It is an alkylating agent derived from nitrogen mustard was first synthesized by Arnold and Bourseaux in 1958 (Figure 6).

FIGURE 6

CHEMICAL STRUCTURE OF CYCLOPHOSPHAMIDE



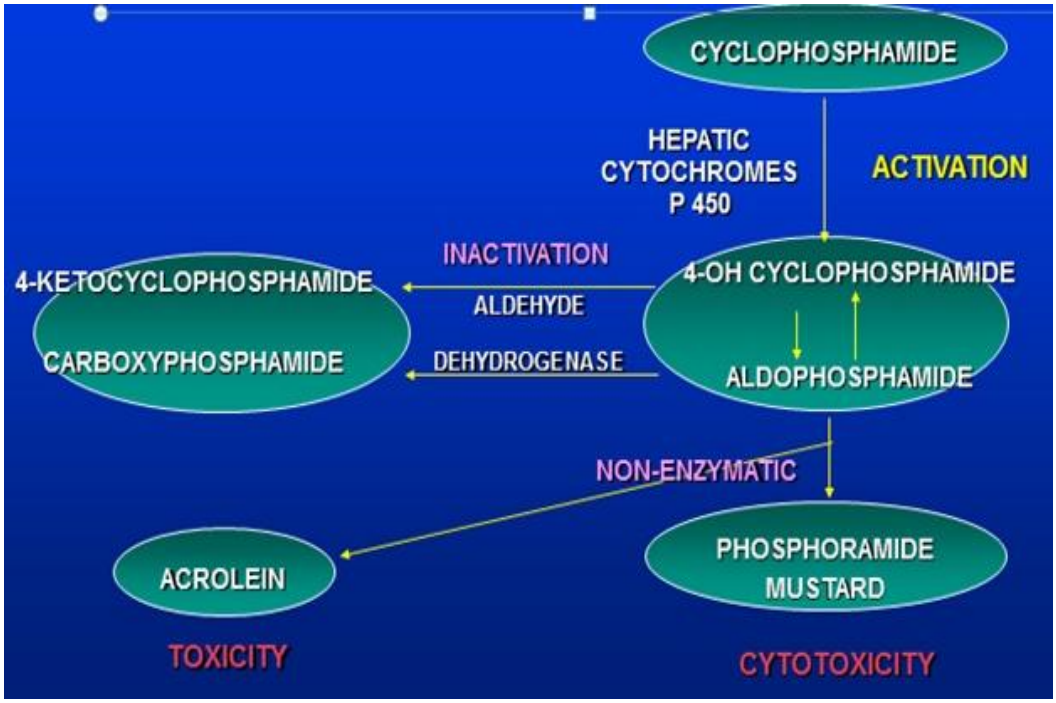
Mechanism of action

Alkylating effects

Cell- cycle non- specific drug, cytotoxic effects are independent of the cell cycle. The primary metabolite of cyclophosphamide form covalent bond with DNA. This alkylation leads to DNA cross linking, abnormal base pair formation, imidazole ring cleavage, with depurination, and chain cessation, leading to cell death by apoptosis (Figure 7).

FIGURE 7

MECHANISM OF ACTION OF CYCLOPHOSPHAMIDE



Immunomodulatory effects

It has a superior effect on B lymphocytes than T lymphocytes, depress B- cell function more than T-cell function. Suppressor T-cells (CD8) affected more than helper T cells (CD4)[56].

Pharmacokinetics

It has 75% bioavailability with peak plasma level occurring 1-2 hour of dosing. It undergoes hepatic metabolism by cytochrome P- 450 system. Plasma half life of 5-9 hour. It is an prodrug, is converted by the liver to 4-hydroxycyclophosphamide and aldophosphamide. Aldophosphamide, in turn cleaved intracellularly to phosphoramide mustard and acrolein. Active metabolites are excreted in urine.

Clinical uses

FDA- Approved indications

Mycosis fungoides

Off-label dermatologic uses

Bullous dermatoses: Pemphigoid, pemphigus

Autoimmune connective tissue diseases

Dermatomyositis

Lupus erythematosis

Scleroderma

Vasculitis

Wegener’s granulomatosis

Polyarteritis nodosa

Leukocytoclastic vasculitis

Cryoglobulinemia

Neutrophilic dermatoses

Pyoderma gangrenosum

Behcet’s disease

Neoplasms

Histiocytosis X

Infiltrative diseases

Scleromyxedema

Miscellaneous

Psoriatic arthritis

Severe eczematous dermatitis

Ichthyosis

Other uses

Rheumatoid arthritis, Nephrotic syndrome, Non-Hodgkin's lymphomas, other lymphoid malignancies, Breast and ovarian cancers and Solid tumors in children.

Contraindications

Absolute

Pregnancy (category: D)

Lactation

Hypersensitivity to cyclophosphamide

Depressed bone marrow function

Relative

Infections

Impaired liver function

Impaired kidney function

Cyclophosphamide resistance

Mechanism includes the following:

1) Decreased penetration of the drugs into cells
2) Increased production of competing nucleophilic substances
3) Increased activity of the DNA repair system
4) Increased metabolism to inactive metabolites

Adverse effects

Carcinogenicity

Increased risk of transitional cell bladder carcinoma

Leukaemia, non-Hodgkin's lymphoma, squamous cell carcinoma

Hematological effects

Leukopenia, thrombocytopenia, anaemia, rarely aplastic anaemia

Bladder adverse effects

Dysuria, urgency, microscopic hematuria

Hemorrhagic cystitis (5-40%) - dose related, caused by acrolein metabolite

Increased risk of bladder carcinoma

Bladder fibrosis, necrosis, contracture, vesicoureteral reflux

Drug should be discontinued once hematuria is noted. Advised to drink plenty of fluids and void frequently to decrease the risk of hemorrhagic cystitis. Mesna (sodium 2-mercapto-ethanesulfonate) has been used to reduce this adverse effect when cyclophosphamide has been given in large doses.

Gastrointestinal

Nausea, vomiting, diarrhoea –seen in 70% of patients

Anorexia, stomatitis, hepatotoxicity

Dermatologic adverse effects

Anagen effluvium, pigmented band on teeth

Diffuse hyper pigmentation of skin, transverse ridging of nails, acral erythema, Steven-Johnson syndrome, rarely urticaria, mucosal ulceration

Reproductive

Amenorrhea, azoospermia (irreversible after prolonged therapy)

Other rare adverse effects

Cardiomyopathy (high dose), pneumonitis, interstitial pulmonary fibrosis, SIADH, convulsions, progressive muscular paralysis, fever, anaphylaxis

Opportunistic infections

Drug interactions

Drugs decreases cyclophosphamide serum levels because of increased metabolism are phenobarbital, nevirapine.

Drugs increases cyclophosphamide serum levels and increases myelosuppression are chloramphenicol, thiazides, cimitidine, allopurinol.

Pharmacodynamic interaction involving increased risk of myelosuppression with chlorambucil, zidovudine.

Monitoring guidelines

Baseline

Complete physical examination should be done

Laboratory

Complete hemogram, renal function test, liver function test, blood sugar and urine analysis should be done.

The follow-up

Examination (at least every 6 months)

Complete physical examination and special emphasis on lymph node and cutaneous examination for malignancies. Pap smear for women should be done.

Laboratory

Complete hemogram and urine analysis (stop treatment if red blood cells appear in urine) should be monitored for weekly (frequency reduced to biweekly and monthly if results are unremarkable after 3 months of therapy). Liver function test, renal function test, blood sugar should be monitored for monthly once for 3 months then once in every 3 months.

Periodically (at least every 6 months): Chest x ray and urine cytology

Indications for discontinuing therapy: WBC < 4000-4500 cells/ mm3 or platelets < 100000 cells/mm3, presence of red cells in urine.

MYCOPHENOLATE MOFETIL

It is an first-line immunosuppressive agent for pemphigus and less effective adjunct than azathioprine[57].

Mechanism of action

Non-competitive inhibitor of inosine monophosphate dehydrogenase, blocking de novo purine biosynthesis. Selectively cytotoxic for cells that relay on de novo purine synthesis (i.e. lymphocytes).

Dosage: 30-40 mg /kg / day twice daily

Adverse effects

Gastrointestinal including constipation, diarrhoea, nausea and vomiting, bleeding, myelosuppression, leukopenia, headaches, hypertension, peripheral oedema, infectious disease, lymphoma.

Monitoring guidelines

Baseline complete blood count and complete metabolic profile. Repeat laboratory tests weekly × 6 week, then every 2 week × 2 months, and then monthly. Blood pressure should be monitored.

Contraindications

Absolute:

Patients with severe infections, malignancy

Pregnancy (category: C)

Other drugs used to treat pemphigus are

Dapsone

It is a steroid-sparing drug used in maintenance phase of pemphigus vulgaris. It may be used in conjunction with other immunosuppressive agents particularly rituximab.

Cyclosporine

Cyclosporine (3–6 mg/kg body weight per day) has been used in combination with steroids in patients otherwise unresponsive to moderate doses (1 mg/kg per day) of prednisolone. Cyclosporine suppresses cellular immunity resulting in reduced expression of several lymphokines.

Methotrexate

Moderate doses of methotrexate (10-17.5 mg/week) allowed withdrawal of prednisolone in steroid dependent patients.

Tetracycline

Minocycline and tetracycline have also been used as adjuvants with steroids.

Gold

It is advocated as an adjuvant in refractory pemphigus vulgaris. Auranofin, an oral formulation of gold, is easier to use and less toxic than parenteral formulations.

Rituximab

It is a monoclonal anti- CD20 antibody, approved for therapy of B-cell malignancies. In pemphigus it depletes B-lymphocytes and produced remission in some but not all patients with treatment resistant disease.

Intravenous immunoglobulin

It may be useful as adjuvant therapy in pemphigus patients whose condition does not respond to conventional therapy. It will decreases serum auto antibodies.

Plasmapheresis

Used for severe pemphigus or for pemphigus that is unresponsive to a combination of prednisone and immunosuppressive agents.

SYSTEMIC SCLEROSIS

DEFINITION

Systemic sclerosis or scleroderma (SSc) is a chronic multisystem disease of unknown etiology characterized by skin induration and thickening, accompanied by fibrosis and chronic inflammatory infiltration of internal organs, microvascular damage and dysfunction and immune dysfunction. The name of progressive systemic sclerosis was coined by Goetz in 1945 [58].

Epidemiology

The incidence rates in USA and European countries range between 4.5 - 18.7 new cases per million[59]. The prevalence is higher in USA and Australia than in Japan and Europe. Systemic sclerosis is also predominant in females, with the female-to-male ratio ranging between 5:1 and 14:1. The age of onset is most commonly in the range of 30–50 years. It is uncommon in children less than 13 years.

AETIOLOGY

Autoimmunity

Antinuclear antibodies present in over 80% of patients and specific auto antibodies - anti-isotopomerase (22%) and anticentromere (up to 30%) suggests an autoimmune response.

Genetic factors

Abnormalities of the serum immunoglobulin and high rate of antinuclear factor in the first-degree relatives of patients with systemic sclerosis, increased incidence of HLA-B8 in more severe cases, suggest that genetic factors play a part in the aetiology[60].

Environmental factors

Toxins include solvents – vinyl chloride, benzene, toluene, epoxy resins and drugs like bleomycin, pentazocine, cocaine, docetaxel.

PATHOGENESIS

Abnormal immune response

It is proposed that CD4+ T cells respond to an unidentified antigen accumulate in the skin and release cytokines that activate inflammatory cells and fibroblasts.

Vascular damage

Micro vascular disease is constantly present early in the course of systemic sclerosis and may be the initial lesion. Intimal proliferation is present in 100% of digital arteries of patients. Capillary dilatation with leaking and destruction is also common.

Fibrosis

The progressive fibrosis of the disease may be the cause of multiple abnormalities and scarring.

DIAGNOSIS

The criteria for diagnosis are patients should have either:

1) The single major criteria

Symmetric skin thickening was seen in proximal to the metacarpophalangeal or metatarsophalangeal joints.

2) Two of the three minor criteria consisting of

(a) Sclerodactyly

(b) Digital pitted scarring

(c) Bilateral basal pulmonary fibrosis.

CLASSIFICATION

1. Diffuse cutaneous systemic sclerosis
2. Limited cutaneous scleroderma

Clinical Features

Fibrosis is most obvious in the skin, gastrointestinal tract, lungs, heart, kidneys and numerous vascular structures are frequently involved[60]. The presenting feature commonly is Raynaud's phenomenon. Other features are swelling of the hands and joints and ulceration and gangrene of the fingers.

LABORATORY INVESTIGATIONS

A skin biopsy shows a thinned epidermis and extensive fibrosis of the lower two-thirds of the dermis and extending into the panniculus, replacing the subcutaneous fat. A perivascular mononuclear cell infiltrate may precede fibrosis. The collagen bundles appear pale, homogeneous and swollen.

Anemia may be present in patients with renal failure, malabsorption or gastrointestinal bleeding. The ESR may be raised. A false positive VDRL can be found in around 5% of patients. Anticardiolipin antibodies are found in approximately onefourth of the patients with severe involvement. Rheumatoid factor is positive around 30% of patients.

Antinuclear antibodies (ANAs) have been detected in approximately 85%–98% of patients during the course of the disease. There are three main

subgroups of autoantibodies: anticentromere antibody, anti-DNA topoisomerase 1 antibodies and anti-RNA polymerase 3 antibodies.

TREATMENT OF SYSTEMIC SCLEROSIS

Dexamethasone – cyclophosphamide pulse therapy is the main stay of treatment of systemic sclerosis.

Immunomodulatory drugs

a) Cyclosporine A

It can improve skin indurations but not visceral manifestations.

b) Methotrexate

c) Mycophenolate mofetil

d) Immunoablation/stem cell transplantation

e) Extracorporeal photopheresis

f) Anti-thymocyte globulin

Symptomatic treatment

1. **Vasodilators** : Nifedipine 10-20 mg thrice daily administered orally

Other drugs are oral reserpine, guanethidine, diltiazem and ketanserin.

These drugs may increase the blood flow to the fingers. Prazosin 1mg thrice daily dose administered orally can decrease the frequency and severity of vasospasm. Warming up of hands for five minutes every four hours in a warm water bath may significantly improve Raynauds phenomenon. This technique may decreases the severity and number of attacks of Raynaud's phenomenon.

2. Prostacyclin and iloprost (synthetic prostacyclin analogue) are effective vasodilators and inhibit the aggregation of platelet and have been effective in diminishing the severity, occurrence and extent of Raynaud's phenomenon, relieving pain and healing ischemic ulcers.

3. Intravenous pentoxifylline can improve capillary function and beneficial in acute ischemic lesions.

4. Penicillamine 500-1500 mg / day for 2 years may lessen skin thickness, decrease the rate of further visceral involvement and recover the prognosis of patients if started near the beginning in their disease.

5. Antihypertensive drugs – minoxidil used to decrease the blood pressure in malignant hypertension and captopril can be used in most cases with elevated plasma renin activity. It control blood pressure, improves kidney function and prevents renal failure and death if started in early disease.

6. For reflux esophagitis, ranitidine (150mg b.i.d) or omeprazole (20-60mg/day) are recommended.

Other measures are gastrostomy required for severe dysphagia. Surgical intervention may be required for stricture oesophagus. Breathing exercises and antibiotics used to treat the chest infection. Endothelin inhibitors such as bosenton or sitaxsentan used to treat a serious complication like pulmonary hypertension.

MATERIALS & METHODS

MATERIALS AND METHODS

STUDY CENTRE:

The present study was carried out in the department of Dermatology, Government Rajaji Hospital, Madurai after obtaining clearance from Institutional Ethical Committee, Government Rajaji Hospital, Madurai.

Ref. Letter No. 6681/E4/3/2013 Dated: 14.05.2013.

COLLABORATING DEPARTMENTS:

- Institute of Pharmacology, Madurai Medical College, Madurai
- Department of Dermatology, Government Rajaji Hospital, Madurai
- Department of Ophthalmology, Government Rajaji Hospital, Madurai
- Department of Pathology, Madurai Medical College, Madurai
- Department of Biochemistry, Madurai Medical College, Madurai

STUDY DESIGN:

Single centre, open labelled, prospective, observational study in patients with chronic skin diseases, attending Dermatology department.

STUDY PERIOD:

This study was conducted from February 2013 to August 2014 for a period of 19 months.

1. Literature collection 3 months
2. Designing the study 1 month

3. Case selection and follow-up 12 months
4. Analysis & Interpretation 2 months
5. Discussion 1 month

STUDY MATERIALS:

Drugs used were

- T. Methotrexate 5mg – 25 mg orally weekly once
- Inj. Cyclophosphamide 500 mg iv monthly once - pulse therapy
- Inj. Dexamethasone 100 mg iv for 3 consecutive days at 28 days interval (pulse therapy)
- T. Paracetamol 500mg as required
- T. Ranitidine 150 mg twice daily or C. Omeprazole 20 mg once daily
- T. Calcium once daily
- T. B.complex, folic acid and ferrous sulphate orally in case of anaemia

METHODOLOGY:

80 patients of both sexes attending Dermatology Department were selected by the Dermatologist, Government Rajaji Hospital, Madurai as per the eligibility criteria. From all the patients written informed consent was obtained. Consent forms were dated and signed by both the investigator and the patient.

INCLUSION CRITERIA:

1. **Those newly initiated with immunosuppressant drugs** for the following diseases- Psoriasis, Pemphigus vulgaris & Systemic sclerosis

    - Easy to convince for study
    - No prior exposure to immunosuppressant drugs
    - Unlikely to develop drug related adverse reactions of chronic usage

2. **Age > 18 years**

    Patients can be made to understand easily

    Better cooperation from the patients

    Economical independence

3. **Sex – either sex**

    To monitor the response to treatment in both genders

4. **Subjects willing for the study**

    Subjects were explained about the proposed study and need for follow up. Only those who were willing were enrolled for the study.

EXCLUSION CRITERIA:

1. **Pregnancy**

    Hemodynamic and hormonal changes may alter the disease course. Moreover Immunosuppressant drugs are teratogenic.

2. Lactation

Hemodynamic and hormonal changes may alter the disease course. Moreover Immunosuppressants will be secreted in the breast milk and their immunosuppressive property will enhance the chance of infections.

3. Hepatic impairment

Those with chronic liver diseases are excluded as immunosuppressant drugs can cause hepatic damage and also cause flare up of viral hepatitis.

4. Renal impairment

Those with chronic renal diseases are excluded as drug therapy with immunosuppressants can cause renal damage.

5. Immunodeficiency

Immunosuppressive property will enhance the chance of infections

6. Diabetes mellitus

Corticosteroids can impair glucose tolerance.

Immunosuppressants will enhance the chance of infections in diabetic patients who are already immunocompromised.

7. Chronic infective diseases like Tuberculosis, Leprosy

8. Malignancy

9. Hypertension

10. Concomitant medications

Those patients consuming complementary or alternative medicines internally are excluded from the study.

11. Previous participation:

Those who have participated in similar drug trials elsewhere are excluded

12. Others

Patients were subjected to thorough systemic examination.

If any other abnormalities were detected, they were excluded from the study.

Discontinuation criteria

Patients were permitted to discontinue from the study once they are decided to do so.

80 patients with chronic skin diseases attending dermatology department fulfilling all the above criteria were included in the study. Evaluated with detailed general examination, complete hemogram, erythrocyte sedimentation rate, liver function tests, renal function tests, blood sugar, lipid profile and routine urine examinations were done.

Patients were informed both verbally and in written format by the investigator about the nature, significance, implications and the risks of study prior to enrollment. These were explained by the investigator in a

words and language that were simple to understand by the patient. Informed consent was obtained from all the patients individually dated and signed both by the patient and the examiner. The details of the examiner (name, phone number and contact address) were specified to every patient, to permit them to speak to for any ailments at anytime during the study period. The socio- demographic data, age, sex, address, educational qualifications, occupation, smoking and alcohol intake data were collected at the initial visit.

Efficacy was assessed by using scoring system for the particular diseases. Blood and urine investigations were done, blood pressure was recorded and chest X- rays were taken as per dermatologist's advice. Reports were assessed and medications started after obtaining informed consent. Patients were informed about adverse reactions to drug therapy and were given the investigator's details for reporting.

Patients attended dermatology department every fortnight to procure drugs. During these visits, compliance was checked by counting empty drug packs and patients with poor compliance were given counselling to adhere to therapy. Dose modifications were done according to response. Adverse reactions to drugs were assessed. Investigations were carried out in cases of adverse reactions and appropriate therapy instituted.

The autoimmune diseases included in the study are psoriasis, pemphigus vulgaris and systemic sclerosis. Patients with psoriasis were

treated with methotrexate, pemphigus vulgaris and systemic sclerosis patients were treated with dexamethasone – cyclophosphamide pulse therapy. In patients with psoriasis the treatment efficacy was monitored by Psoriasis Area Severity Index (PASI) score. In patients with pemphigus vulgaris the treatment efficacy was monitored by Pemphigus Area and Activity Score (PAAS) and in patients with systemic sclerosis the treatment efficacy was monitored by modified Rodnan's skin score (MRSS) at first, third and sixth month of therapy.

The tolerability of drugs was monitored by assessing adherence to treatment, adverse reactions complained by the patients. Laboratory investigations like complete hemogram, erythrocyte sedimentation rate, liver and renal function tests, lipid profile, and urine routine were monitored at baseline, first, third and sixth month of therapy. The results were tabulated and analyzed statistically.

STATISTICAL ANALYSIS

The data were analyzed with SPSS statistical software package (Version 16.0 SPSS Inc., Chicago, USA) and analysed using descriptive statistics and Friedman test for skewed data. P value < 0.05 was considered to be statistically significant.

RESULTS

RESULTS

80 patients with chronic skin diseases were recruited for the study and analyzed for the response to drug therapy and adverse reactions. All the 80 patients were followed up to the end of the study. There was no drop out from the study.

Among the 80 patients included in the study, the age related distribution were as follows, 17(21.25%) patients were in the age group 20-29 years, 26(32.5%) patients belonged to the age group of 30-39 years, 26(32.5%) patients in 40-49 years, 7(8.75%) belonging to 50-59 years and 4(5%) patients were above 60 years. The majority of patients belonged to 30-49 years of age (65%). The distribution in relation to age and gender is shown in table as follows.

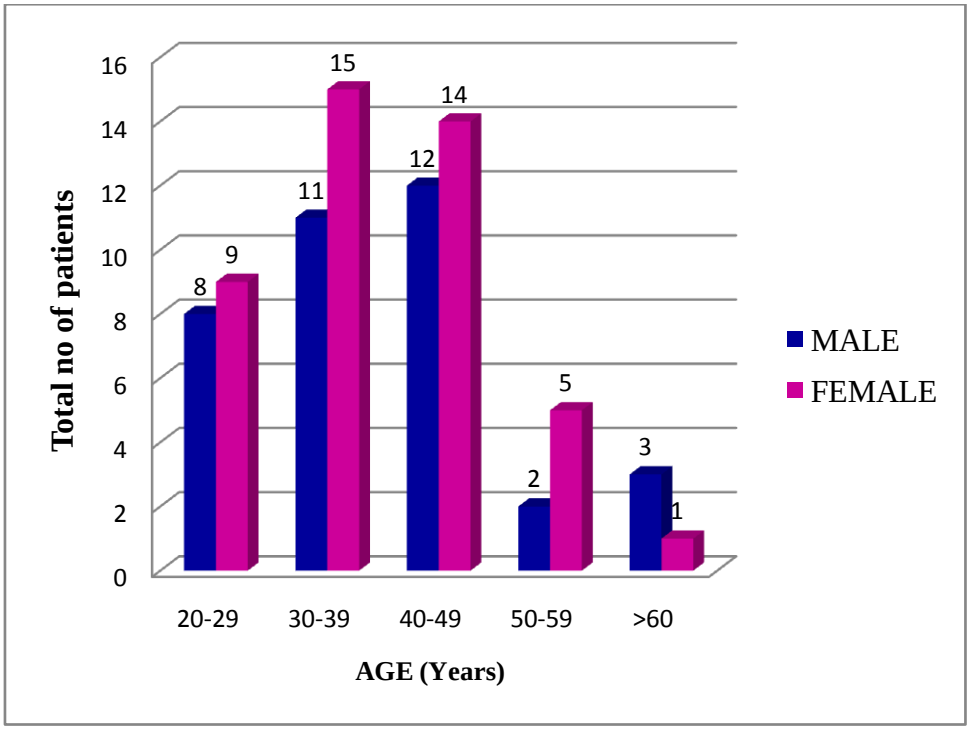
TABLE 1: AGE AND GENDER DISTRIBUTION OF CHRONIC SKIN DISEASES

AGE (YEARS)	MALE	FEMALE	TOTAL NO OF PATIENTS
20 – 29	8	9	17
30 – 39	11	15	26
40 – 49	12	14	26
50 - 59	2	5	7
> 60	3	1	4
TOTAL	36	44	80

Patients belonging to 30-39 years and 40-49 years of age were predominant (N=26) followed by patients in age of 20-29 years (N=17). The mean age of the subjects was 38.69 ± 10.67 years (Figure 8).

FIGURE 8

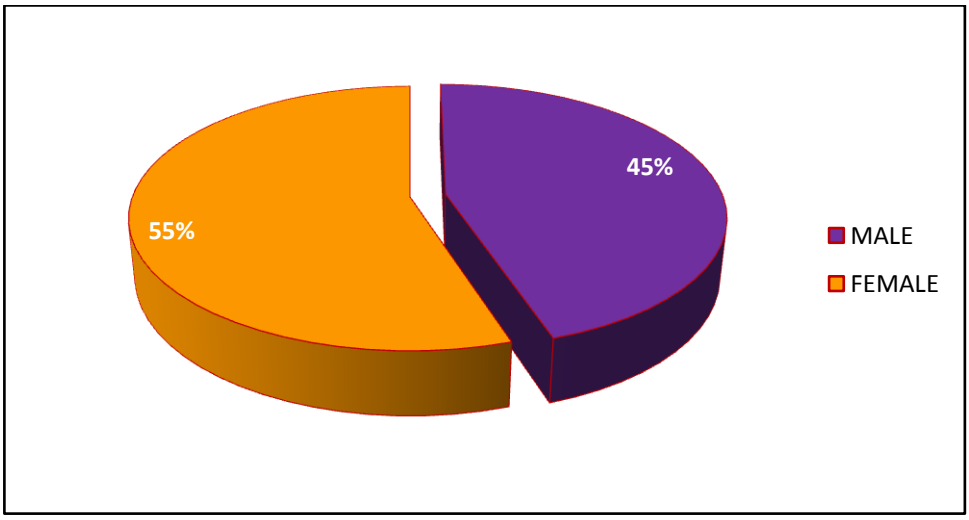
AGE AND GENDER DISTRIBUTION OF CHRONIC SKIN DISEASES



Among the 80 patients analyzed, 45% were males and the rest were females (55%). This data on gender distribution is represented in figure 9.

FIGURE 9

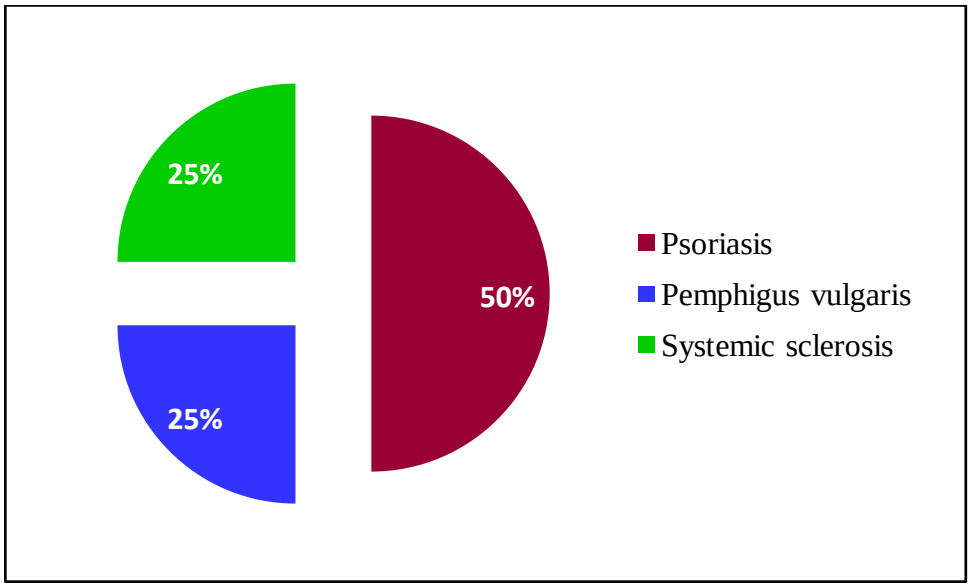
GENDER DISTRIBUTION OF CHRONIC SKIN DISEASES



Among the 80 patients included in the study, 40 patients had psoriasis, 20 patients pemphigus vulgaris and 20 patients systemic sclerosis (Figure 10).

FIGURE10

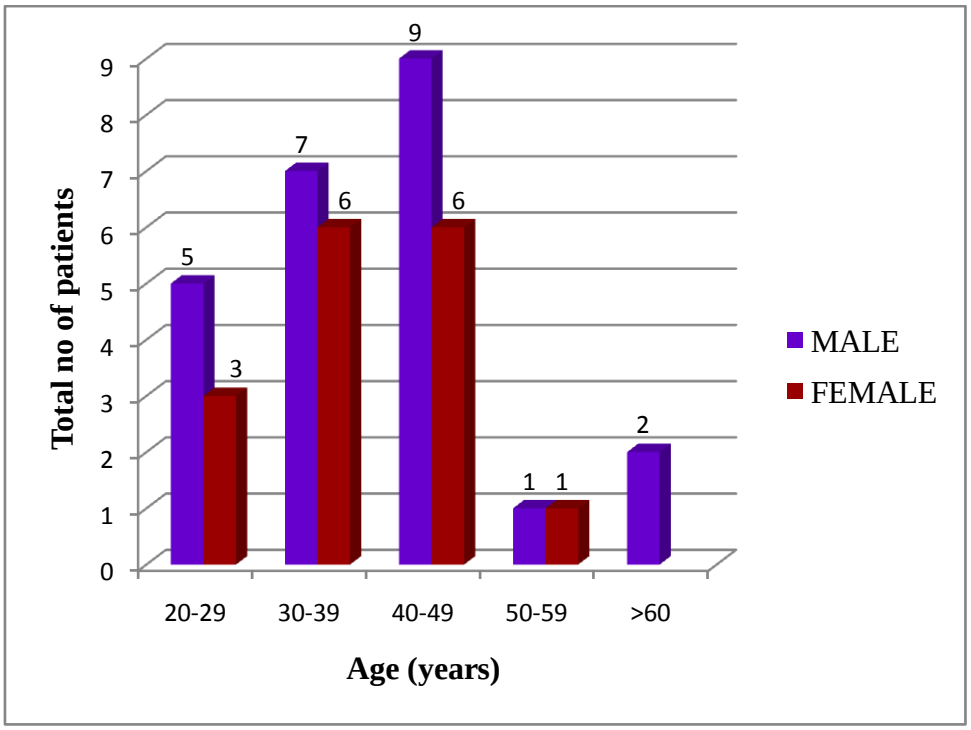
PERCENTAGE DISTRIBUTION OF CHRONIC SKIN DISEASES



Among 40 psoriasis patients analyzed, patients belonging to 40-49 years of age were predominant (N=15) followed by patients in age of 30-39 years (N=13). The mean age of the subjects was 38.8 ± 10.37 years. Among the 40 patients, 60% were males and the rest were females (40%) (Figure 11).

FIGURE 11

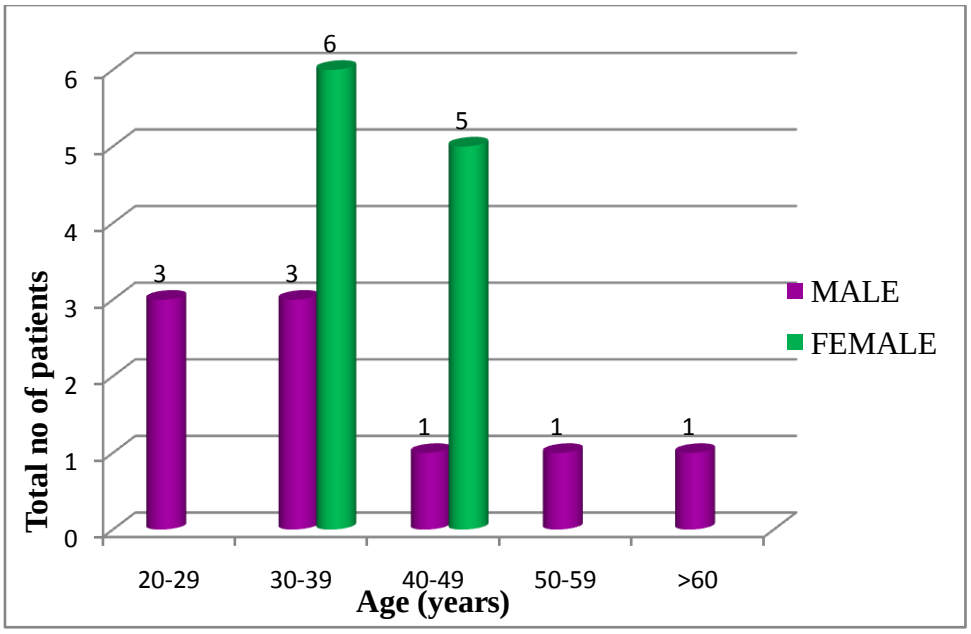
AGE AND GENDER DISTRIBUTION OF PSORIASIS



Among 20 pemphigus vulgaris patients analyzed, patients belonging to 30-39 years of age (N=9) followed by patients in the age of 40-49 years (N=6). The mean age of the subjects was 37.7 ± 9.69 years. Among them 45% were males and 55% were females (Figure 12).

FIGURE 12

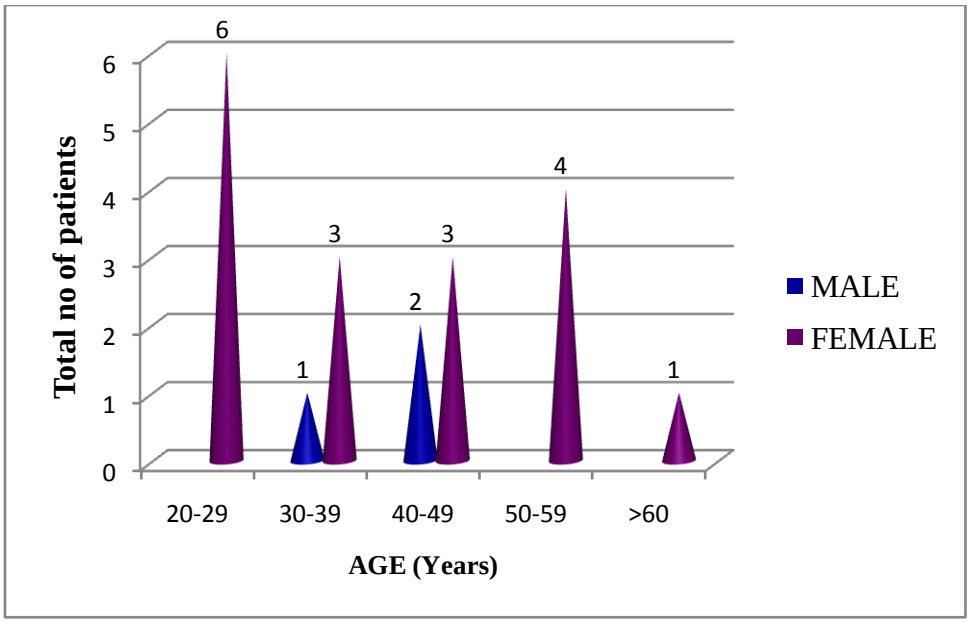
AGE AND GENDER DISTRIBUTION OF PEMPHIGUS VULGARIS



Among 20 systemic sclerosis patients analyzed, patients belonging to 20-29 years of age (N=6) were predominant followed by patients in age of 40-49 years (N=5). The mean age of the subjects was 39.45 ± 12.04 years. Among them 15% were males and 85% were females (Figure 13).

FIGURE 13

AGE AND GENDER DISTRIBUTION OF SYSTEMIC SCLEROSIS



PARAMETERS FOR ASSESSING THE EFFICACY OF THE DRUG THERAPY:

PASI score for the evaluation of psoriasis in methotrexate therapy:

Psoriasis Area Severity Index (PASI) score is a useful tool in monitoring the response of psoriasis to methotrexate therapy. Drug therapy has improved the skin lesions as shown by the falling PASI scoring at the end of first, third and sixth months of treatment. The data is represented in the following table and figure 14.

TABLE 2

MEDIAN PASI SCORE OF PSORIASIS

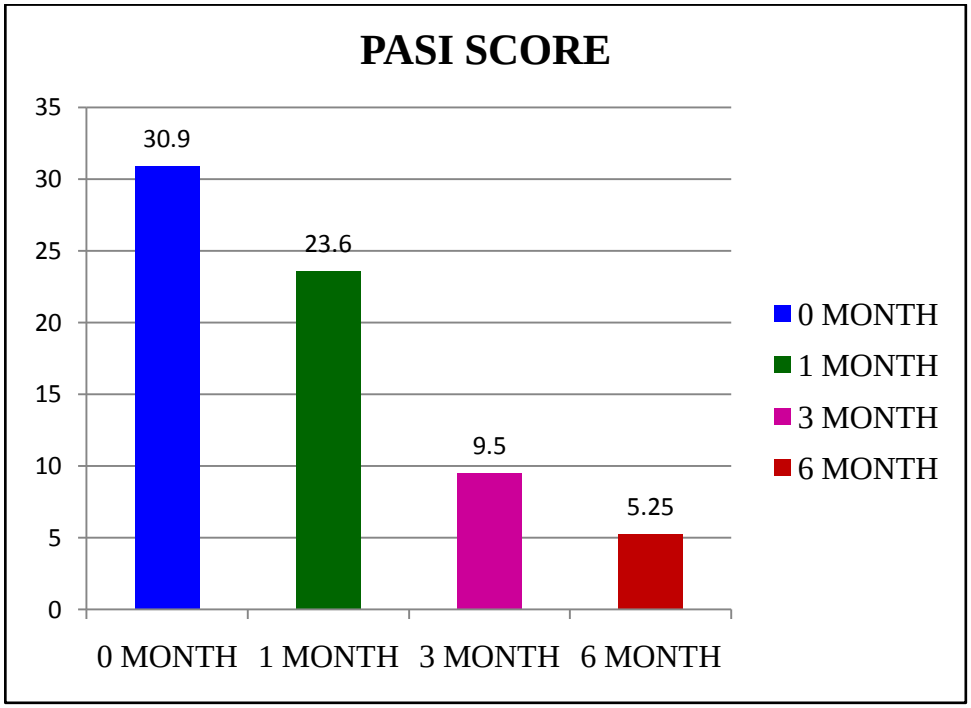
	0 month	1 month	3 months	6 months
PASI(median)	30.90	23.60*	9.50*	5.25*
Standard deviation	7.20	6.59	2.99	2.04

[* = P value < 0.0001]

Application of Friedman's test shows that there was a statistically significant ($p < 0.0001$) decrease in PASI score after one month (median = 23.60), three months (median = 9.50), and six months (median = 5.25) of treatment compared to baseline score (median = 30.90) in psoriasis patients receiving methotrexate. [**$\chi 2(3) = 120.00, p < .0001$].**

FIGURE 14

MEDIAN PASI SCORE OF PSORIASIS



Pemphigus Area and Activity Score (PAAS) for pemphigus vulgaris

Pemphigus Area and Activity Score (PAAS) is useful for monitoring the response of drug therapy to pemphigus vulgaris. Drug therapy with dexamethasone – cyclophosphamide(pulse) has improved the lesions as shown by the falling Pemphigus Area and Activity Score at the end of first, third and sixth months of treatment. The data is represented in the following table and figure 15.

TABLE 3

MEDIAN PAAS IN PEMPHIGUS VULGARIS

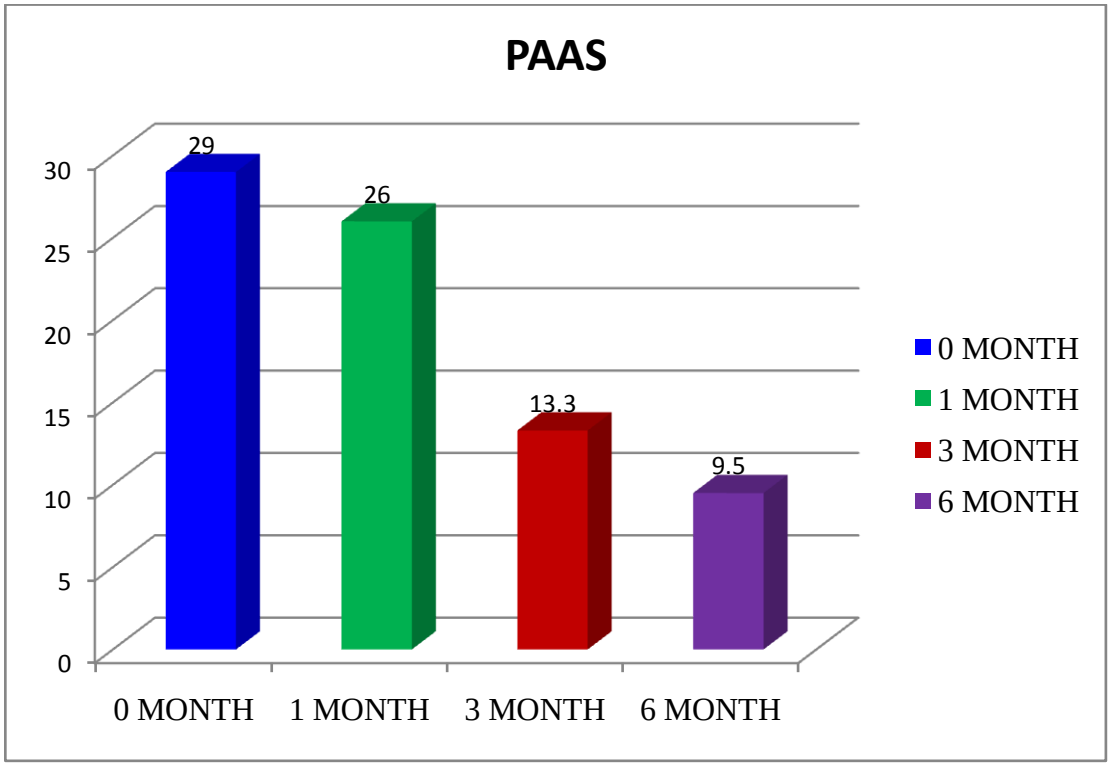
	0 month	1 month	3 months	6 months
PAAS(median)	29.00	26.00*	13.30*	9.50*
Standard deviation	7.85	7.72	4.71	2.24

[* = P value < 0.0001]

Application of Friedman's test shows that there was a statistically significant decrease(P value < 0.0001) in Pemphigus Area and Activity Score after one month (median = 26), three months(median = 13.30), six months(median =9.50) of treatment compared to baseline score (median = 29) in Pemphigus Vulgaris patients treated with Dexamethasone – Cyclophosphamide pulse therapy. **[χ2(3) = 58.860, p < .0001].**

FIGURE 15

MEDIAN PAAS IN PEMPHIGUS VULGARIS



Modified Rodnan Skin Score for systemic sclerosis

Modified Rodnan Skin Score (MRSS) is useful for assessing the drug therapy to systemic sclerosis. Drug therapy with dexamethasone – cyclophosphamide (pulse) has improved the skin lesions as shown by the falling modified Rodnan Skin Score at the end of first, third and sixth months of treatment. The data is represented in the following table and figure 16.

TABLE 4

MEDIAN MRSS IN SYSTEMIC SCLEROSIS

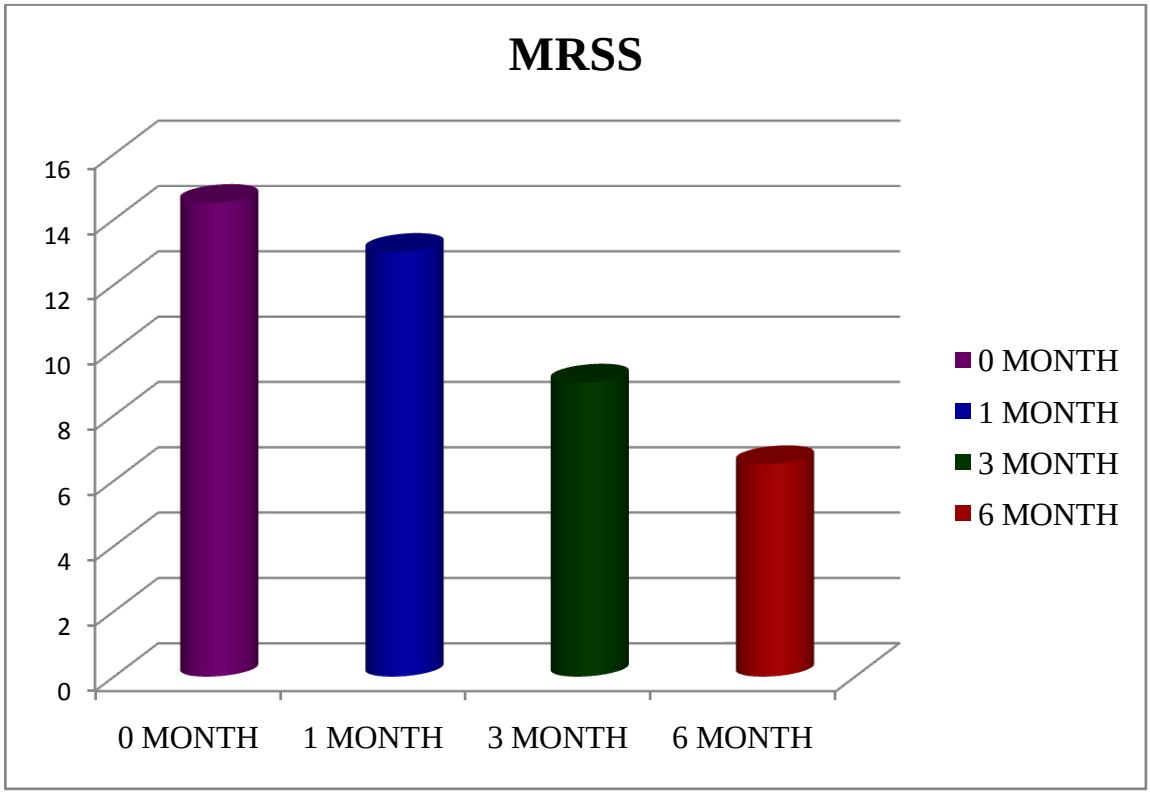
	0 month	1 month	3 months	6 months
MRSS(median)	14.50	13.00*	9.00*	6.50*
Standard deviation	6.59	6.23	4.89	3.46

[* = P value < 0.0001]

Application of Friedman's test shows that there was a statistically significant ($p < 0.0001$) decrease in Modified Rodnan Skin Score after one month (median = 13), three months (median = 9), and six months (median = 6.50) of treatment compared to baseline score (median = 14.50) in systemic sclerosis patients treated with Dexamethasone – Cyclophosphamide pulse therapy. [$\chi 2(3) = 60.00, p < .0001$].

FIGURE 16

MEDIAN MRSS IN SYSTEMIC SCLEROSIS



ADVERSE EFFECTS OF IMMUNOSUPPRESSANT DRUGS USED IN CHRONIC SKIN DISEASES:

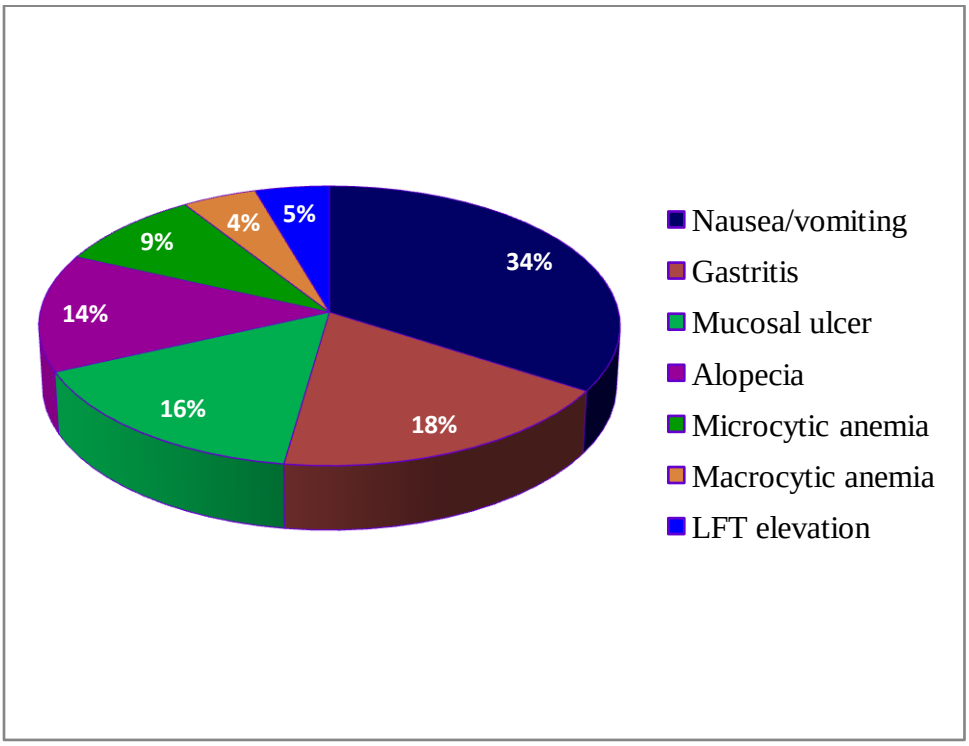
This was assessed by history, general examination, systemic examination, ophthalmological examination and laboratory investigations like complete hemogram, erythrocyte sedimentation rate, liver and renal function tests, lipid profile, and urine routine during drug therapy periodically.

ADVERSE EFFECTS OF METHOTREXATE THERAPY IN PSORIASIS

Psoriasis patients treated with methotrexate study group 34% reported with nausea/vomiting, 18% of gastritis, 16% of mucosal ulcer, 14% of alopecia, 9% microcytic anaemia with minimal side effects like macrocytic anaemia (4%), and liver enzyme elevation (5%). Methotrexate induced adverse reactions reported in the study population of psoriasis was represented in the following pie diagram (Figure 17).

FIGURE17

ADVERSE REACTIONS OF METHOTREXATE

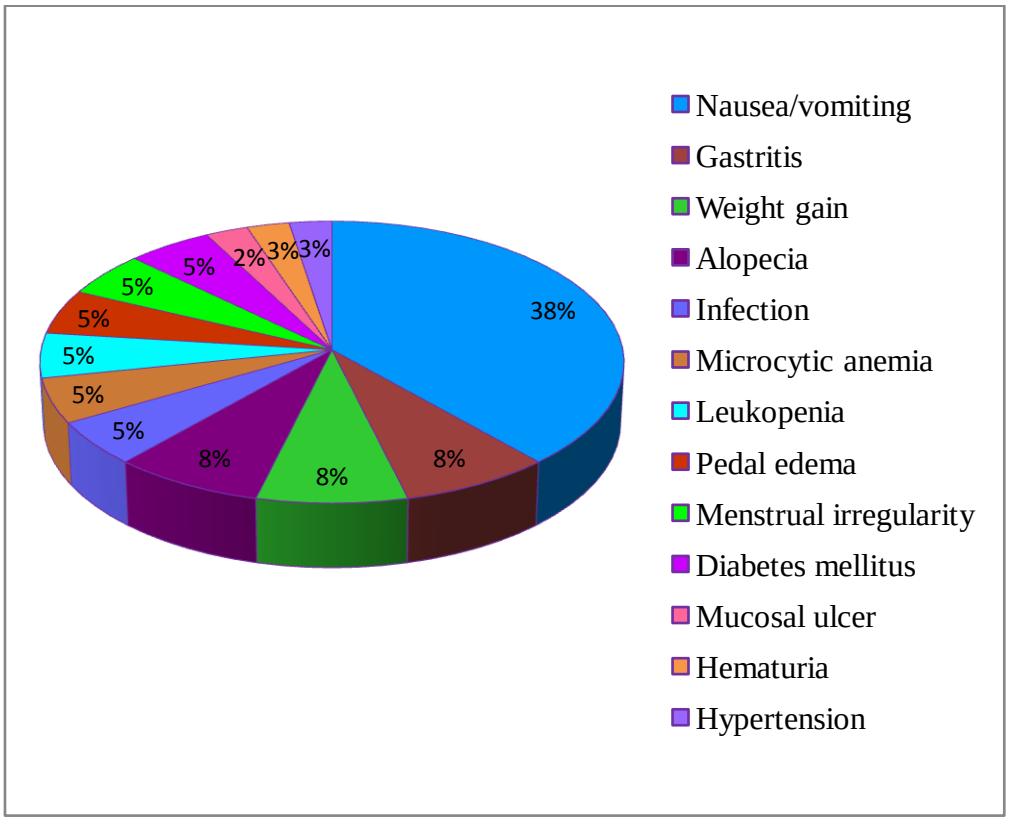


ADVERSE EFFECTS OF DCP THERAPY IN PEMPHIGUS VULGARIS:

The study group of pemphigus vulgaris patients treated with dexamethasone – cyclophosphamide pulse therapy, 38% reported with nausea/vomiting, 8% of gastritis, 8% weight gain, 8% alopecia with minimal side effects of 5% infection, 5% microcytic anaemia, 5% pedal edema, 5% menstrual irregularity, 5% diabetes mellitus, 3% hypertension, 3% hematuria, 2% mucosal ulcer. Dexamethasone – cyclophosphamide pulse therapy and azathioprine induced adverse reactions reported in the study population of pemphigus vulgaris was represented in the following pie diagram. (Figure18).

FIGURE 18

ADVERSE REACTIONS OF DCP THERAPY IN PEMPHIGUS VULGARIS

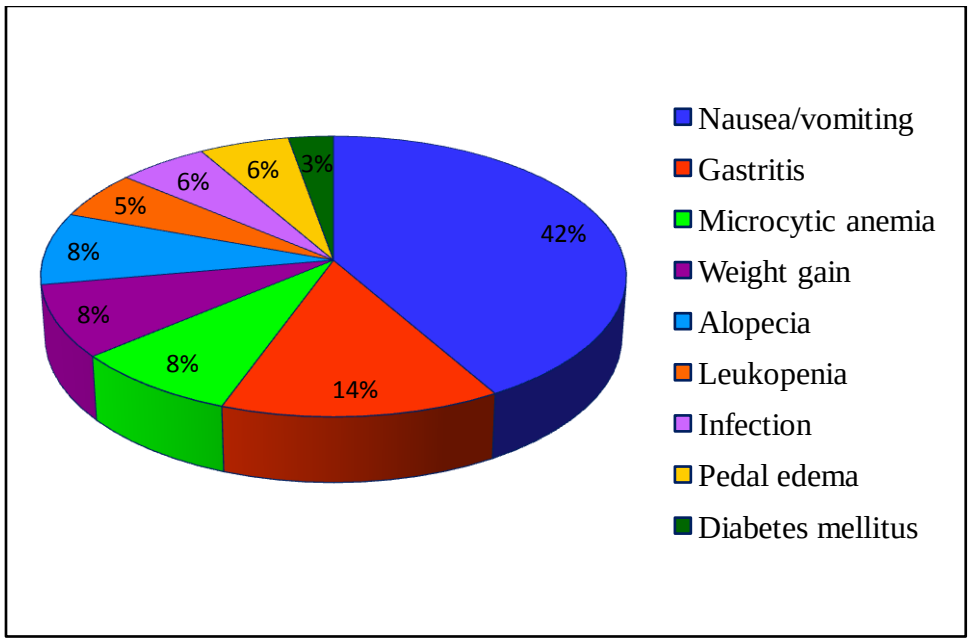


ADVERSE EFFECTS OF DCP PULSE THERAPY IN SYSTEMIC SCLEROSIS

The study group of systemic sclerosis patients treated with DCP therapy, 42% reported with nausea/vomiting, 14% of gastritis, 8% alopecia, 8% microcytic anemia, 8% weight gain with minimal side effects of 6% pedal edema, 6% infection and 3% diabetes mellitus. DCP therapy induced adverse reactions reported in the study population of systemic sclerosis was represented in the following pie diagram (Figure19).

FIGURE 19

ADVERSE REACTIONS OF DCP THERAPY INSYSTEMIC SCLEROSIS



Adverse effects reported with these immunosuppressant drugs include gastric intolerance, majority of the patients had nausea/vomiting followed by gastritis and anaemia. The management of adverse reactions included dose reduction and pharmacological therapy like anti emetics used to treat nausea/vomiting, gastritis treated by proton pump inhibitor, mucosal ulcer & anaemia treated by folic acid, iron and vitamin B12 supplementation, infection treated by oral antibiotics. Diabetes mellitus managed by insulin therapy.

DISCUSSION

DISCUSSION

Skin diseases are extremely common affecting up to 20 to 30% of individuals at any one time in the general population. Chronic skin diseases includes autoimmune skin diseases like psoriasis, bullous disorders, systemic sclerosis, systemic lupus erythematosus, dermatomyositis and inflammatory dermatoses like atopic and seborrheic dermatitis.

Autoimmune skin diseases are managed with corticosteroids in the early days. The extensive use of steroids often results in disabling and life threatening adverse effects. The concomitant use of immunosuppressive agents have reduced the steroid usage in these diseases and are associated with better treatment outcome and decreased adverse effect of both the drugs. So this study aims at monitoring the clinical response of south Indian population with chronic skin diseases attending a tertiary care hospital, along with monitoring the tolerability and safety of Immunosuppressive therapy in the above patients.

80 chronic skin disease patients of both genders who were diagnosed as autoimmune skin diseases attending dermatology department were selected for the study. Among the 80 patients included in the study, 40 patients had psoriasis, 20 patients had pemphigus vulgaris and 20 patients had systemic sclerosis.

Systemic therapies for psoriasis which are in common use, includes Psoralen - UVA (PUVA) therapy, retinoids and immunosuppressant's like

methotrexate and cyclosporine[61]. Methotrexate was introduced as a therapy for psoriasis in 1958 and it remains one of the oldest and most widely used systemic therapy for all types of psoriasis. It acts by competitive inhibition of dihydrofolate reductase. Intra cellular polyglutamation of methotrexate and increased formation of adenosine is a key factor for clinical efficacy in psoriasis by its anti-inflammatory, anti proliferative and immunosuppressant action. The weekly dose of methotrexate in psoriasis patients varies from 5 mg to 25 mg. It starts with the minimal dose, so called test dose of 5 or 7.5 mg for a week and followed by the blood samples for complete hemogram and liver function tests are taken for a possible occurrence of side effects. The most risky was myelosuppression, which could be dangerous to the patient. If the investigations are within normal levels, the dose of methotrexate could be increased. Laboratory parameters are monitored frequently (complete blood count, hepatic enzymes and renal parameters) and the patient is examined for possible side effects on skin and mucous membrane. The dose is adjusted according to the requirements.

Efficacy of the methotrexate drug therapy was assessed by Psoriasis Area Severity Index (PASI) score. Scoring was done before starting the methotrexate therapy and at the end of first month, third month and sixth month of therapy. The study shows that there is a statistically significant ($p < 0.0001$) decrease in PASI score after first month, three months and six months of treatment with methotrexate compared to baseline score. This

finding supports that Haustein et al. in a 26 year retrospective study found methotrexate to be highly efficacious in their 75% psoriasis patients while Heydendael et al. observed > 75% reduction in the mean PASI score at 16 weeks in all their 43(100%) patients[62].

In the present study methotrexate induces adverse effects like gastro intestinal upset in the form of nausea, vomiting (34%), gastritis (18%) followed by mucosal ulcer (16%), microcytic anaemia (9%) and liver enzyme elevation (5%). The mechanism of nausea/vomiting is due to direct stimulation of chemoreceptor trigger zone by the drug, as well as generation of emetic impulses from the upper gastro intestinal tract. These side effects were managed by dose reduction, addition of anti emetics and proton pump inhibitors. Microcytic anaemia is mainly due to depression of bone marrow function. Anaemia was treated by folic acid and iron supplementation. An elevated liver enzyme comes to normal after dosage reduction of methotrexate.

Pemphigus vulgaris is the next common autoimmune skin disease. The mainstay of the treatment is systemic corticosteroids. Following the introduction corticosteroid treatment in the 1950s, the mortality rate of patients with pemphigus declined from 90% to 24%. Prolonged and high dosage corticosteroid treatment may lead to many undesirable effects. Corticosteroid pulse therapy and immunosuppressive drugs were

administered in an effort to diminish the undesirable effects of conventional daily dose regimens. This therapy has reduced the mortality.

Intravenous administration of mega dose steroids and immunosuppressants (pulse therapy) has the rationale to obtain the immunosuppressive effects quickly while avoiding the side effects associated with long term use of the drugs. The two most commonly used immunosuppressive agents are azathioprine (2mg/kg) and cyclophosphamide (1-2mg/kg) given orally in between the pulse therapy.

Pasricha and Gupta introduced DCP treatment in the therapeutic regimen for pemphigus in 1982, and achieved long term remissions in his patients of pemphigus by using DCP therapy. DCP composed of 100 mg dexamethasone dissolved in 5% dextrose 500 ml given as an intravenous infusion for 2 hours, repeated on 3 successive days. On the second day, the patients in addition received 500 mg of cyclophosphamide added to the dexamethasone infusion. This constituted one DCP. The DCPs were repeated after exactly 28 days from the first day of the drip. Any divergence from the 28 day cycle was considered as irregular treatment. They also received oral cyclophosphamide 50 mg per day.

Cyclophosphamide is an alkylating agent[63], inhibits the lymphopoietic cells without affecting the hemopoietic cells. In high dose these drug is selectively toxic to B lymphocytes. It inhibits cyclical production of antibody producing B lymphocytes in autoimmune diseases.

Corticosteroids acts by anti-inflammatory and immunosuppressive property. Azathioprine affects T and B cell function, T-cell mediated function is decreased, antibody production by B cell is diminished.

The efficacy of the DCP pulse therapy was assessed by Pemphigus Area and Activity Score (PAAS). PAAS is calculated individually for cutaneous and mucosal lesions, the total score is calculated by totalling the values. PAAS values can range from 0.8 up to 50 in the severe cases. The present study shows that there is a statistically significant ($p < 0.0001$) reduction in PAAS score after 1 month, three months, six months of treatment compared to baseline score Significant clinical improvement has also been reported in other studies. Sacchidanand et al. reported remission in 41 (82%) patients in their study of 50 patients of auto immune bullous disease treated with DCP therapy[64]. Pasricha et al. achieved remission in all the 103 pemphigus patients treated with DCP therapy[65].

The main side effects observed in the present study with dexamethasone – cyclophosphamide pulse therapy are nausea/vomiting (38%), gastritis (8%), weight gain (8%), microcytic anaemia (5%), infection (5%). These drugs cause gastritis by reducing prostaglandin synthesis in gastric mucosa. Nausea/vomiting are due to the stimulation of CTZ by the drug as well as generation of emetic impulses from the upper gastro intestinal tract. Ondansetron (8 mg) was administered for treatment of nausea/ vomiting and gastritis was managed by addition of proton pump

inhibitors. Anaemia is treated by folic acid and iron therapy. Oral candidiasis and secondary pyogenic infection of the skin are treated with oral nystatin and systemic antibiotics. Leukopenia was observed in 5% of our patients, cyclophosphamide was withheld for a period of 2 weeks and white blood cell counts improved and cyclophosphamide was then restarted. Leukopenia is due to myelosuppression of the alkylating drug.

Two new cases (5%) of diabetes mellitus were diagnosed in previously healthy patients receiving the DCP regimen and were started on insulin therapy. The mechanism of development of diabetes mellitus was due to the increased glucose output from liver, resistance to insulin and inhibition of glucose utilization by peripheral tissues. One patient developed hypertension and was managed with suitable antihypertensive drugs. One patient had microscopic haematuria, in whom cyclophosphamide was stopped and replaced with azathioprine.

Systemic sclerosis is an autoimmune disease characterized by vascular abnormalities, connective tissue sclerosis and atrophy, and the presence of auto antibodies that result in fibrosis and vascular abnormalities.

Systemic sclerosis patients also treated with dexamethasone-cyclophosphamide pulse therapy for monthly once like pemphigus vulgaris. Cyclophosphamide is immunosuppressive alkylating agents which suppresses and modulates lymphocytes by modification of cellular components. Patients were evaluated biweekly during the first month and

then monthly once for 6 months. The evaluation of treatment included clinical and laboratory analysis (complete blood counts, serum electrolytes, blood sugar, liver enzymes and urine analysis) before and after each DCP therapy.

The efficacy of the DCP drug therapy in systemic sclerosis was assessed by Modified Rodnan Skin Score (MRSS), the most commonly used scoring system. The study shows that there is a statistically significant ($p < 0.0001$) decrease in Modified Rodnan Skin Score after first month, third month and sixth month of DCP therapy compared to baseline score.

The finding supports that Steen and Medsger finding in their study series of 278 patients with reduction in at least 25% of the skin scores compared to the initial value also presented a 90% survival in 5 years[66]. Similarly the analysis performed in its series by Valentine et al. demonstrated the beneficial effect of cyclophosphamide in the treatment of cutaneous involvement in patients with early disease with approximate reduction of 30% in the MRSS. Hence we concluded that cyclophosphamide reduced the severe cutaneous thickening in patients with diffuse systemic sclerosis and could in future have beneficial effects in morbidity and mortality of the disease.

In the present study the main adverse effects observed with DCP therapy in systemic sclerosis are nausea/vomiting (42%), gastritis (14%), alopecia (8%), microcytic anaemia (8%). These side effects are managed by

administration of anti emetics, proton pump inhibitor, folic acid and iron supplementation. Oral nystatin and systemic antibiotics were used to treat the oral candidiasis and secondary pyogenic infection of the skin. One new case (3%) of diabetes mellitus was diagnosed in previously healthy patients receiving the DCP regimen and they were started on insulin therapy.

The study concluded that methotrexate therapy in psoriasis used in our centre was highly efficacious and caused minimal adverse effects and it was well tolerated. DCP therapy in pemphigus vulgaris and systemic sclerosis was well tolerated and produced significant clinical response to drug therapy.

SUMMARY

&

CONCLUSION

SUMMARY AND CONCLUSION

Chronic skin diseases include autoimmune skin diseases like psoriasis, bullous disorders, systemic sclerosis, systemic lupus erythematosus and dermatomyositis. Many autoimmune diseases are more common among women than men. It starts at a relatively young age and continue throughout life. Most of the diseases are chronic in nature requiring a life time care.

The efficacy of drug therapy and its tolerability among south Indian patients is unknown. Hence the present study was undertaken with approval of Institutional Ethical Committee to monitor the efficacy and adverse effects of immunosuppressant drugs in patients with autoimmune diseases.

Autoimmune skin diseases are managed with corticosteroids in the early days. The extensive use of steroids often results in disabling and life threatening adverse effects.

80 chronic skin disease patients of both genders who were diagnosed as autoimmune skin diseases attending dermatology department were selected for the study. Among the 80 patients included in the study, 40 patients had psoriasis, 20 patients pemphigus vulgaris and 20 patients systemic sclerosis. Psoriasis patients were managed with methotrexate therapy. Pemphigus vulgaris & systemic sclerosis patients were managed with dexamethasone- cyclophosphamide pulse therapy.

The study group was followed bi-weekly for a period of six months. The compliance was checked and adverse reactions monitored by clinical examination, haematological and urine examination.

The study group showed good response to drug therapy which was assessed by relevant scoring system like PASI score for methotrexate therapy in patients with psoriasis, Pemphigus Area and Activity Score for dexamethasone- cyclophosphamide pulse therapy in patients with pemphigus vulgaris, and modified Rodnan skin score for DCP therapy in patients with systemic sclerosis.

The adverse effects observed in the study were managed by the following measures like proton pump inhibitors were added to prevent peptic ulcer, ondansetron (8 mg) was administered for treatment of nausea and vomiting. Calcium and vitamin D were supplemented to reduce osteoporotic effects of steroids. Folic acid and iron therapy were used to treat patients with anaemia. Oral candidiasis and secondary pyogenic infection of the skin are treated with oral nystatin and systemic antibiotics.

From this study we conclude that extensive use of conventional daily steroids often results in disabling and life threatening adverse effects. The concomitant uses of immunosuppressant drugs like methotrexate, dexamethasone- cyclophosphamide pulse therapy were well tolerated and efficacious in autoimmune skin diseases.

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ANNEXURES

PROFORMA

Name: Age: Sex: Address:

OP.No / IP.No:

H/O Skin diseases:

Duration of therapy:

H/O any other drug intake:

H/O adverse drug reaction:

Family history:

Menstrual history:

General examination:

Systemic examination:

TO MONITOR DRUG EFFICACY:

1) Psoriasis Area and Severity Index (PASI) Score for psoriasis
2) Pemphigus Area and Activity Score (PAAS) for pemphigus vulgaris
3) Modified Rodnan Skin Score (MRSS) for systemic sclerosis

TO MONITOR ADVERSE EFFECTS:

Adherence to treatment

METHOTREXATE:

Nausea	Vomiting	Diarrhoea
Fatigability	Decreased appetite	Oral ulcer
Pruritis	Rashes	Alopecia
Myalgia	Headache	Fever
Jaundice	Cough	

CYCLOPHOSPHAMIDE:

Nausea	Vomiting	Diarrhoea
Fatigability	Decreased appetite	H/O Infection
H/O Haematuria	Dysuria	Urgency
Alopecia	Oral ulcer	Cough
Palpitation	Bleeding	Amenorrhoea
Urticaria	Hyper pigmentation	Skin rash
Jaundice	Convulsion	

AZATHIOPRINE:

Nausea	Vomiting	Diarrhoea
Abdominal pain	Fatigability	H/O Infection
H/O Bleeding	Jaundice	Alopecia
Fever	Rashes	Myalgia
Joint pain		

DEXAMETHASONE:

Nausea	Vomiting	Abdominal pain
Increased appetite	Weight gain	H/O Infection
Delayed wound healing	Striae	Hirsutism
Cataract	Glaucoma	Myopathy
Diabetes	Hypertension	Fracture
Menstrual irregularity	Psychosis	Depression

INVESTIGATIONS

1) **BLOOD**
    - Complete hemogram
    - Liver function tests
    - Renal function tests
    - Blood glucose
    - Lipid profile
    - Serum electrolytes
    - Elisa test for HIV
2) URINE ROUTINE
3) X RAY CHEST- PA VIEW
4) ECG
5) OPHTHALMIC EVALUATIONS

MONITORING DRUG EFFICACY BY SCORING SYSTEM

I.Psoriasis Area Severity Index Score (PASI) for Methotrexate

PSORIASIS AREA AND SEVERITY INDEX (PASI) WORKSHEET

HOSPITAL NO.: ... .
PATIENT NAME: ... .
DATE OF VISIT: ... .

The Psoriasis Area and Severity Index (PASI) is a quantitative rating score for measuring the severity of psoriatic lesions based on area coverage and plaque appearance.

Plaque characteristic	Lesion score	Head	Upper Limbs	Trunk	Lower Limbs
Erythema	0 = None 1 = Slight 2 = Moderate 3 = Severe 4 = Very severe				
Induration/Thicknes					
Scaling					
Ad together each of the 3 scores for each body region to give 4 separate sums (A).					
Lesion Score Sum (A)					

Percentage area affected	Area score	Head	Upper Limbs	Trunk	Lower Limbs
Area Score (B) Degree of involvement as a percentage for each body region affected (score each region with score between 0-6)	0 = 0% 1 = 1% - 9% 2 = 10% - 29% 3 = 30% - 49% 4 = 50% - 69% 5 = 70% - 89% 6 = 90% - 100%				
Multiply Lesion Score Sum (A) by Area Score (B), for each body region, to give 4 individual subtotals (C).					
Subtotals (C)					
Multiply each of the Subtotals (C) by amount of body surface area represented by that region, i.e. x 0.1 for head, x 0.2 for upper body, x 0.3 for trunk, and x 0.4 for lower limbs.					
Body Surface Area		**x 0.1**	**x 0.2**	**x 0.3**	**x 0.4**
Totals (D)					
Ad together each of the scores for each body region to give the final PASI Score.					

PASI Score = [ ]

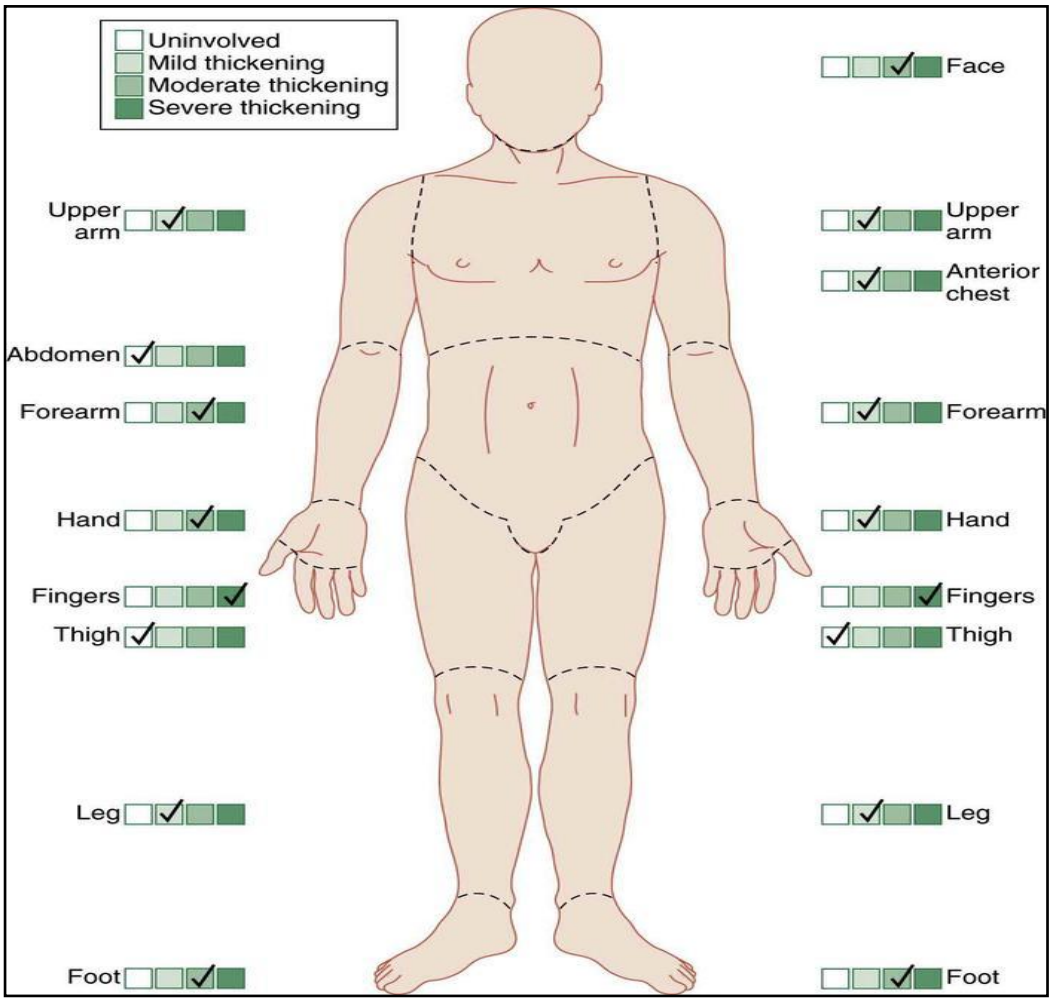
Total score = 72

II. Pemphigus Area and Activity Score (PAAS) for Dexamethasone-Cyclophosphamide Pulse Therapy in Pemphigus Vulgaris

Cutaneous lesions							
Clinical markers	Clinical scores						
	0	1	2	3	4	5	6
A: Activity							
a No. of new blisters per day	0	1–5	6–10	11–20	>20	.	.
b Peripheral extension of existing blisters	Nil	Mild	Moderate	Extensive	.	.	.
c Nikolsky's sign	Negative	Perilesional	Distant	.	.	.	.
B: Area (%)	Nil	0–15	16–30	31–50	51–70	71–90	>90
Head score (H) = [(a + b + c)× score of area]× 0.1, trunk score (T) = [(a + b + c)× score of area]× 0.3, upper limb score (UL) = [(a + b + c)× score of area]× 0.2, lower limb score (LL) = [(a + b + c)× score of area]× 0.4; total score (0–15) = H + T + UL + LL							
Mucous membranes							
Markers	Clinical scores						
	0		1	2		3	
Area	Nil		1 site	2 sites		>2 sites	
Severity	Nil		Mild	Moderate		Severe	
Mucous membrane score (0–6) = area score + severity score							

Total (PAAS) score = Cutaneous score + Mucous membrane score

III. Modified Rodnan Skin Score (MRSS) for Dexamethasone-Cyclophosphamide Pulse Therapy in Systemic Sclerosis



MRSS is assessed by skin thickness at 17 different areas

Total score = 51

INFORMED CONSENT FORM IN ENGLISH

Full name of the patient (in capital letters): _____

Address: _____ Date of Birth: _____

Patient no: _____ Sex: _____ I freely agree to participate in the above – mentioned clinical study.

My doctor _____ informed me in a personal counselling interview about the study drug, possible side effects and risks, the nature, objective and significance of this clinical study and my responsibilities resulting thereof. In addition, I read and understood the contents of the Patient Information Sheet and Informed Consent Form. The doctor answered all questions in an adequate and comprehensible manner. I had sufficient time to decide on my participation in this clinical study.

I will follow the instruction of my doctor, which are essential for the performance of this clinical study. I have the right to withdraw from the study at any time without giving any reason and without any disadvantage for me. I confirm that I have not participated in this study and I have not taken part in another study within the last 30 days prior to the start of the study.

I received one original of the Patient Information Sheet together with the signed Information Consent Form.

(Place, Date & Signature of the Patient)

(Place, Date & Signature of the Doctor)

PATIENT INFORMATION SHEET

Who can be contacted for further questions?

For further questions regarding this clinical study or your rights as patient and participant in the study, please contact your doctor who will always be ready to provide you the necessary information.

If you have experienced any health related problems as well as in case of hospitalization please contacts your doctor.

Name and Address of the Contact Person: _____

_____

_____

_____

Phone number: _____

Please take a copy of this information sheet home with you.

PATIENT INFORMATION SHEET AND INFORMED CONSENT FORM IN TAMIL

நோயாளிகளின் தகவல் மற்றும் ஒப்புதல் படிவம்

ஆய்வு தலைப்பு :-

நாள்பட்ட தோல்வியாதிக்கு பயன்படுத்தப்படும் இம்முனோசப்ரசண்ட் மருந்துகளின் பாதுகாப்பு மற்றும் திறத்தன்மையை சோதிப்பதற்கான ஆய்வு:

நோயாளி அடையாளப்படுத்துதல் :

பங்கேற்பாளர் சுருக்கொப்பம் :

பங்கேற்பாளர் எண :

பங்கேற்பாளர் பிறந்த தேதி/வயது :

ஒரு ஆராய்ச்சி ஆய்வில் பங்கேற்கும்படி நீங்கள் கேட்டுக்கொள்ளப்பட்டு வருகிறீர்கள். பங்குபெற உங்களுக்கு விருப்பமா என்பதை முடிவு செய்ய உங்களுக்கு உதவ, இந்த ஒப்புதல் படிவம் தகவல்களைக் கொண்டுள்ளது. நேரம் எடுத்துக்கொண்டு, இந்தப் படிவத்தைக் கவனமாக படித்து, உங்களுக்கு இருக்கும் ஏதேனும் கேள்விகளை ஆய்வு மருத்துவரையோ அல்லது ஊழியர்களையோ கேட்கவும்.

இந்த ஆய்வைப் பற்றி :-

- நாள்பட்ட தோல் வியாதியின் சிகிச்சைக்கு பயன்படுத்தப்படும் மருந்துகளின் திறத்தன்மையை மதிப்பீடு செய்வதற்கு.
- நாள்பட்ட தோல் வியாதியின் சிகிச்சைக்காக பயன்படுத்தப்படும் மருந்துகளின் பாதுகாப்பு மற்றும் தாங்குதிறனை சோதித்துப் பார்ப்பதற்கு.

இந்த ஆய்வில் பங்கேற்க நீங்கள் அனுமதிக்கப்படுவதற்கு சில காரணங்கள் இருக்கக்கூடும்.

- நீங்கள் 18 வயதிற்கு மேற்பட்டவர்
- இந்த ஆய்வில் பங்கேற்க தாங்கள் சமீப காலத்தில் தோல்வியாதியினால் பாதிக்கப்பட்டவராகவும் மற்றும் தோல்வியாதிக்கு வேறு எந்த மருந்தும் எடுக்காதவராகவும் இருப்பீர்கள்.

இந்த ஆய்வில் பங்கேற்க நீங்கள் அனுமதிக்கப்படாததற்கு சில காரணங்கள் இருக்கக்கூடும். இக்காரணங்களுள் சில :-

- நீங்கள் 18 வயதைவிடக் குறைவானவர் அல்லது 70 வயதை விட அதிகமானவர்

- ஆய்வினூடே, நீங்கள் கருவுற்றிருக்கிறீர்கள் தாய்ப்பால் கொடுத்துக் கொண்டிருக்கிறீர்கள்

- நீரிழிவு நோயால் பாதிக்கப்பட்டு இருப்பீர்கள்

- சிறுநீரகம் அல்லது கல்லீரல் பாதிக்கப்பட்டவராக இருப்பீர்கள்

நான் என்ன செய்யுமாறு கேட்டுக்கொள்ளப்படுவேன்?

ஆய்வில் நீங்கள் பங்கேற்றால் நீங்கள் பின்வருவனவற்றைச் செய்ய வேண்டியிருக்கும்.

- இரண்டு வாரங்களுக்கு ஒருமுறை வந்து மருந்து மாத்திரைகளை வாங்கிக் கொள்வது.

- அறிவுறுத்தப்பட்ட படியே ஆய்வு மருந்துக்களை எடுத்துக்கொள்வது.

- வருகைக்கு இடையே உங்களுக்கு ஏதேனும் பக்கவிளைவுகள் இருக்கிறதா என்பதை சோதித்துப் பார்ப்பதற்காக ஆய்வு ஊழியர்களிடம் இருந்து தொலைபேசி அழைப்புகளைப் பெற்றுக்கொள்வது.

- நீங்கள் ஒவ்வொரு முறை வரும்போதும் நீங்கள் எடுத்துக் கொண்டுள்ள மருந்துகளின் காலி அட்டைகளை (பெயருடன் கூடிய அட்டை) எடுத்து வருவது.

நீங்கள் உங்களது ஆய்வு வருகைகளுக்கு வரும்போது ஆய்வு மருத்துவரோ அல்லது ஊழியர்களோ பின்வருபவற்றுள் எதையாவது அல்லது எல்லாவற்றையுமோ செய்யக்கூடும்.

1. உங்கள் மருத்துவ வரலாற்றை மறு ஆய்வு செய்வது

2. ஆய்வு மருந்தையும் அறிவுறுத்தல்களையும் வழங்குவது.

3. உங்களது முக்கிய அடையாளங்களை பரிசோதித்தல் (இதயத்துடிப்பு வீதம், இரத்த அழுத்தம்)

4. இரத்தம் மற்றும் சிறுநீர் மாதிரிகள் சேகரித்தல்

5. உங்கள் உயரம் மற்றும் எடையை சோதிப்பது.

6. ஓர் ஈ.சி.ஜி பரிசோதனை நடத்துவது (இலக்ட்ரோ கார்ட்டியோகிராம் உங்கள் இதயத்தின் மின் செயல்பாட்டின் ஓர் அளவீடு)

இச்சோதனைகள் உங்கள் உடல்நலத்தை கண்காணிக்கப்பயன்படுத்தப்படும்.

மருந்துகள் எப்போதாவது பின்விளைவுகளை உண்டாக்கலாம்

- குமட்டல்/வயிற்று அசௌகரியம்
- வயிற்றுப்போக்கு/ இளகியமலம்
- வாந்தி எடுத்தல்
- பார்வை மங்குதல்
- தசைவலி
- தலைசுற்றல் மற்றும் தலைவலி
- பொதுவான பலவீனம்
- ஒவ்வாமை தோல்பின்விளைவுகள்
- இரத்தச் சிவப்பணுக்கள் இல்லாமல் இருப்பது அல்லது எண்ணிக்கை குறைவாக இருப்பது (இரத்தசோகை)
- இரத்த வெள்ளைஅணுக்கள் இல்லாமல் இருப்பது. ஆல்லது எண்ணிக்கை குறைவாக இருப்பது (நோய்த்தொற்றுக்களை எதிர்த்தும் போராடுகிற அணுக்கள்)
- இரத்தத் தட்டணுக்குகள் இல்லாமல் இருப்பது அல்லது குறைவாக இருப்பது (உங்களுக்கு இரத்தக் கசிவு ஏற்படும் போது உங்கள் இரத்தத்தை உறையச் செய்ய உதவுகிற அணுக்கள்)
- மஞ்சள் காமாலை மற்றும் (மஞ்சள்தோல்) அரிதான நிலைகளில் ஈரல் கோளாறுக்குக் கொண்டு சென்றுவிடுகிற ஹெப்பட்டைட்டிஸ்
- தோல் கரப்பான், அரிப்பு மற்றும் சுவாசிப்பதில் அல்லது முழுங்குவதில் சிரமத்தை ஏற்படுத்தக்கூடிய, முகம், உதடுகள், நாக்கு மற்றும் தொண்டையின் வீக்கம் உள்ளிட்ட கடுமையானதான இருக்கக் கூடிய ஒவ்வாமைப் பின் விளைவுகள்.

ஆய்வின் போது உங்களுக்கு ஒவ்வாமைப் பின்விளைவுகள் ஏற்பட்டால், ஆய்வு மருத்துவத்தை எடுத்துக் கொள்வதை நிறுத்திவிட்டு

உங்கள் ஆய்வு மருத்துவரை உடனடியாக அழையுங்கள்.உங்களுக்கு ஏற்பட்டுள்ள ஒவ்வாமைப் பின்னளைவுகளுக்கு சிகிச்சை அளிப்பதற்கு உங்கள் ஆய்வு மருத்துவர் ஓர் மருந்தைப் பரிந்துரைத்து, உங்கள் நோயிற்கு வேறு ஒரு மருத்துவத்தைப் பரிந்துரைக்கலாம்.

இரத்தப் பரிசோதனைகளின் ஆபத்துகள்:

பெரும்பாலானவர்களுக்கு இரத்தம் எடுப்பதற்காக ஊசி குத்துவது எவ்வித மோசமான பிரச்சனைகளையும் ஏற்படுத்துவதில்லை ஆயினும். சில நேரங்களில் அவை இரத்தம் எடுக்கப்பட்ட இடத்தில் இரத்தக் கசிவு இரத்தம் கன்றிப் போதல் அசௌகரியம் நோய்தொற்றுக்கள் வலி ஆகியவற்றை உண்டாக்கலாம் உங்களுக்கு தலைசுற்றலும் ஏற்படும்.

எலட்ரோகார்டியோக்ராம் / ஈ.சி.ஜி

எலட்ரோகார்டியோக்ராம் /ஈ.சி.ஜிக்கள் பரிசோதனைகள் இதயத்துடிப்பு அல்லது இதய தாளத்தின் மின்சார தடமறிதல்களாகும் அவை ஈகேஜி பரிசோதனைகள் எனவும் அழைக்கப்படுகின்றன. ஒரு ஈசிஜி பரிசோதனை செய்து கொள்வதற்கு உங்கள் உடலின் பல்வேறு பகுதிகளில் ஒட்டுக்கள் வைக்கப்படும்.

எக்ஸ்ரேகதிர் படம் பிடித்தல். :

இந்த ஆய்வின் போது உங்களது நுரையீரல் எக்ஸ் கதிர் படம் எடுக்கப்படும். எக்ஸ் கதிா படங்கள் எடுக்கப்படும் போது நம் உடலானது ஊறு விளைவிக்கும் அயனியாக்கக் கதிர்வீச்சுகளுக்கு உட்படுத்தப்படுகிறது. ஆயினும் ஒரு படம் எடுக்கப்படும் போது வெளிப்படும் கதிர் இயக்கத்தின் அளவு மிகக்குறைவானதாகும் இதனால் நம் உடலுக்கு எவ்வித பாதிப்புகளும் ஏற்படாது.

<u>உலகளாவிய தரவுகள் பாதுகாப்பு அறிக்கை:</u>

இந்த ஆராய்ச்சி ஆய்வை நடத்துவதன் ஒரு பகுதியாக உங்கள் மருத்துவத் தகவல்களை ஆய்வு மருத்துவர் தவிர பிறருடன் பகிர்ந்து கொள்வது அவசியமாகிறது. உங்கள் தனிப்பட்ட ஆரோக்கியத் தகவல்கள் எவ்வாறு பயன்படத்தப்படும் மற்றும் இந்த ஆராய்ச்சி ஆய்வுக்காக அவை யாருக்குத் தரப்படும் (வெளிப்படுத்துதல்) என்பவை பற்றி தரவுகள்

பாதுகாப்பு அறிக்கை விளக்கமளிக்கிறது உங்கள் தனிப்பட்ட ஆரோக்கியத் தகவல்களைப் பார்வையிட உங்கள் உரிமைகள் உட்பட உங்களது பாதுகாப்பு உரிமைகளையும் இது விவரிக்கிறது.

நீங்கள் யார் என்று கண்டறியப் பயன்படுத்தபடும் உங்களைப் பற்றிய தகவல்களே உங்கள் தனிப்பட்ட ஆரோக்கியத் தகவல்களாகும். இந்த ஆய்விற்குத் தேவைப்படும் தற்போதைய உங்கள் மருத்துவப் பதிவேடுகளில் உள்ள தகவல்கள் இந்த ஆய்வின்போது உருவாக்கப்படும் அல்லது சேகரிக்கப்படும் புதிய தகவல்கள் ஆகியவற்றை உள்ளடக்கியவையே இந்த ஆராய்ச்சி ஆய்விற்குத் தேவையான தகவல்களாகும்.

இந்த ஆய்விற்கான ஒப்புதல் படிவத்தில் கையொப்பமிடுவதன் வாயிலாக இந்த தரவுகள் பாதுகாப்பு அறிக்கையில் விவரிக்கப்பட்டுள்ள உங்கள் தனிப்பட்ட ஆரோக்கியத் தகவல்களின் பயன்பாட்டுக்கும் வெளிப்படுத்துதலுக்கும் நீங்கள் அனுமதி (“அங்கீகாரம்”) அளிக்கிறீர்கள் இப்பயன்பாடுகளை நீங்கள் அனுமதிக்க விரும்பவில்லை என்றால். இந்த ஆய்வில் நீங்கள் பங்கேற்க வேண்டாம்.

இந்த ஆராய்ச்சி ஆய்வில் பங்கேற்க நீங்கள் ஒப்புக்கொண்டால் உங்கள் தனிப்பட்ட ஆரோக்கியத் தகவல்கள் கீழ்க்கண்ட வழிகளில் பயன்படுத்தப்படும் மற்றம் வெளிப்படுத்தப்படும்

ஆய்வின் போது ஆய்வை நடத்துவதற்காக உங்கள் மருத்துவப் பதிவேடுகளையும் உருவாக்கப்பட்ட அல்லது சேகரிக்கப்பட்ட தகவல்களையும் ஆய்வு மருத்துவர் மற்றும் ஊழியர்கள் பயன்படுத்துவார்கள்.

உங்கள் ஆய்வுத் தரவுகளை இந்நாட்டிற்கு வெளியேயும் அனுப்பப்பட வேண்டியிருக்கும் இந்நாட்டுச் சட்டங்களால் அளிக்கப்படும் அதே

வகையான பாதுகாப்புகள் கொண்ட இரகசியச் சட்டங்கள் பிற நாடுகளில் இல்லாமல் போகலாம் இருப்பினும் இந்தத் தரவுகள் பாதுகாப்பு அறிக்கையை எல்லா நாடுகளிலம் நிறுவனம

ஆய்வு மருத்துவர் அனுப்பும் ஆய்வுத் தரவுகளில் உங்களை நேரடியாக அடையாளம் காணக்கூடிய வகையில் உங்கள் பெயர் முகவரி அல்லது மற்ற தகவல்களள் இருக்காது மாறாக ஆய்வுத் தரவுகளுக்கு ஓர் குறியீட்டு எண்ணை அளிப்பார் மற்றும் உங்கள் பெயரின் முதலெழுத்துக்களை ஆய்வு மருத்துவர் உபயோகிக்கலாம் ஆய்வு நிறுவனத்திற்கு அனுப்பப்படும் ஆய்வுத் தரவுகளில் உங்களை அடையாளம் கண்டறியும் வகையில் (எ.டு.பிறந்த தேதி) உபயோகிக்கப்படும் (மற்ற தகவல்களையும் சேர்த்து) சில தகவல்கள் இருக்கலாம் பிறரிடம் தரக்கூடிய குறிப்பிட்ட ஆரோக்கியத் தகவல்கள் பற்றிய கேள்விகள் இருக்கலாம் பிறரிடம் தரக்கூடிய குறிப்பிட்ட ஆரோக்கியத் தகவல்கள் பற்றிய கேள்விகள் உங்களுக்கு இருப்பின் அவற்றை பற்றி ஆய்வு மருத்துவரை நீங்கள் கேட்க வேண்டும்

ஒப்புதல் படிவத்தில் விவரிக்கப்பட்ட ஆய்வின் அறிவியல் நோக்கங்களுக்கு ஆதரவளிக்கும் ஆராய்ச்சிக் காரணங்களுக்காகவும் ஆய்வில் சேர்க்கப்பட்ட மருந்து அல்லது சிகிச்சையின் பாதுகாப்பு மற்றும் பலன்களை மதிப்பீடு செய்யவும் ஆய்வில் சேர்க்கப்பட்டுள்ள நோய்(கள்) பற்றி சிறப்பாக புரிந்து கொள்ளவும் அல்லது எதிர்கால ஆய்வுகளை வடிவமைத்து மேம்படுத்தவும் இந்த ஆய்வுத் தரவுகளை பயன்படுத்தப்படும்.

இந்த நாட்டில் மற்றும் யுனைடெட் ஸ்டேட்ஸ் உட்பட பிற நாடுகளில் உள்ள ஒழுங்குமுறை அதிகாரிகள் இந்த ஆய்வில் பங்கேற்கும் மற்ற நிறுவனத்தின் மருத்துவர்கள் மற்றும் ஆய்வை மேற்பார்வையிடும் நன்னெறி மறு ஆய்வு வாரியத்தனர் ஆகியோருடன் உங்கள் ஆய்வுத்தரவுகள் தனியாகவோ அல்லது மற்ற ஆய்வுகளின் தரவுகளின் இணைத்தோ பகிர்ந்து கொள்ளப்படும்.

உங்களை அடையாளம் காணாத ஆய்வுத் தரவுகள் மருத்துவ இதழ்களில் வெளியிடப்படலாம் அல்லது அறிவியல் விவாதங்களின் ஒரு பகுதியாக மற்றவர்களுடன் பகிர்ந்து கொள்ளப்படலாம்

ஆய்வை மேற்பார்வையிடும் நன்னெறி மறுஆய்வு வாரியம் மற்றும் இந்நாட்டில் மற்றும் அல்லது யுனைட்டெட் ஸ்டேட்ஸ் உட்பட பிற நாடுகளிலுள்ள ஒழுங்குமுறை அதிகாரிகள் ஆகியோர் உங்களை நேரடியாகக் கண்டறியும் தகவல்களைக் கொண்டுள்ள உங்கள் மூல மருத்துவப்பதிவேடுகளை மறு ஆய்வு செய்வார்கள். நடத்தப்படும் ஆய்வின் தரம் மற்றும் ஆய்வுத் தரவுகள் அல்லது சட்டத்தால் அங்கீகரிக்கப்பட்ட பிற பயன்பாடுகளை உறுதி செய்வதே இந்த மறு ஆய்வுகளின் நோக்கமாகும்.

சட்டப்படி தேவைப்பட்டால் அல்லது நீங்கள் எழுத்தின் மூலமாக தனியாக ஒப்புதலை வழங்கினால் அன்றி தனிப்பட்ட் ஆரோக்கியத் தகவல்களை ஆய்வு நிதியுதவியளிப்பவர் காப்பீட்டு நிறுவனங்களுக்கு வெளிப்படுத்தமாட்டார்கள்.

உங்கள் மருத்துவ பதிவேடுகள் மற்றும் ஆய்வுத் தரவுகள் கணினிகளில் வைக்கப்பட்டு செயல்முறைப்படுத்தப்படலாம்.

ஆராய்ச்சி ஆய்வு தொடர்பான உங்கள் தனிப்பட்ட ஆரோக்கியத் தகவல்கள் ஆய்வு மருத்துவரிடம் அல்லது ஆராய்ச்சி நிறுவனத்தில் இருக்கும்வரை அவற்றை நீங்கள் பார்வையிடவும் அவற்றின் நகலைப் பெறவும் உங்களுக்கு உரிமையுண்டு இருப்பினும் ஆய்வின் அறிவியல் ஒருமைப்பாட்டை உறுதிசெய்யும் பொருட்டு ஆய்வு முடிவடையும் வரை சில ஆய்வுத் தகவல்களை நீங்கள் மறுஆய்வு செய்ய முடியாது.

ஆய்வு மருத்துவருக்கு எழுத்து மூலம் அறிவிப்பை அளித்து உங்கள் அங்கீகாரத்தை எப்போது வேண்டுமானாலும் நீக்கிவிடலாம் நீங்கள் உங்கள் அங்கீகாரத்தை நீக்கிக் கொண்டால் ஆய்வின் அறிவியல் ஒருமைப்பாட்டை பாதுகாப்பதற்காக ஆய்வு மருத்துவர் அல்லது ஊழியர்கள் இந்த ஆய்வுடன் தொடர்புடைய உங்கள் தனிப்பட்ட மருத்துவத் தகவல்கள் சிலவற்றை பயன்படுத்தும் அல்லது உரிமை வழங்கல் தேவை இல்லாதவரை உங்கள் ஆய்வு மருத்துவர் அல்லது ஊழியர்கள் உங்கள் தனிப்பட்ட ஆரோக்கியத் தகவல்களைப் பயன்படுத்தவோ அல்து வெளிப்படுத்தவோ மாட்டார்கள். ஆனால் உங்கள் அங்கீகாரத்தை நீக்குவதற்கு முன்னர் சேகாரிக்கப்பட்ட ஆய்வுத் தரவுகளை ஆய்வு நிறுவனம்

பயன்படுத்திக்கொள்ளும் நீங்கள் உங்கள் அங்கீகாரத்தை நீக்கிக் கொண்டால் அதன்பிறகு ஆய்வில் நீங்கள் பங்கேற்க முடியாது இருப்பினும் உங்கள் அங்கீகாரத்தை நீக்கி ஆய்விலிருந்து விலகிவிட நீங்கள் முடிவெத்தாலும் கூட உங்களுக்கு அபராதம் ஏதும் விதிக்கப்படாது அல்லது வேறு வகையில் உரிமையுள்ள பலன்கள் எதையும் நீங்கள் இழக்கமாட்டீர்கள்.

நோயாளி தகவல் மற்றும் ஒப்புதல் படிவம்

இணைப்பு :

ஆய்விடத் தகவல் மற்றும் தொடர்பு விவரங்கள்.

நாள்பட்ட தோல்வியாதிக்கு பயன்படுத்தப்படும் இம்முனோ சப்ரசண்ட் மருந்துகளின் பாதுகாப்பு மற்றும் திறத்தன்மையை சோதிப்பதற்கான ஆய்வு:

ஆரோக்கிய அனுபவங்களை அறிவிக்க, ஏதேனும் மற்ற விவரங்களைப் பற்றி கேட்பதற்கானஆய்வு மருத்துவர்களின் தொடர்பு விவரங்கள்

ஆய்வு மருத்துவரின் பெயர்

முகவரி

தொடர்பு எண்

ஓர் பங்கேற்பாளராக உங்கள் உரிமைகளைப் பற்றி கேட்பதற்கான ஈஆர்பி தொடர்பு விவரங்கள்

ஈஆர்பி தொடர்பு நபரின் பெயர்

தொடர்பு எண்

நோயாளி தகவல் மற்றும் ஒப்புதல் படிவம்:

இணைப்பு :

நாள்பட்ட தோல்வியாதிக்கு பயன்படுத்தப்படும் இம்முனோ சப்ரசண்ட் மருந்துகளின் பாதுகாப்பு மற்றும் திறத்தன்மையை சோதிப்பதற்கான ஆய்வு:

இந்தப் பக்கத்தை கையொப்பமிடுவதன் மூலமாக பின்வருவனவற்றை நான் உறுதி செய்கிறேன்.

மேற்படி ஆய்விற்கான ..... தேதியிடப்பட்ட இந்த நோயாளி தகவல் மற்றும் ஒப்புதல் படிவத்திலுள்ள அனைத்துத் தகவல்களையும் நான் படித்துப் புரிந்து கொண்டிருக்கிறேன் எனவும் அதைப்பற்றி சிந்திக்க எனக்கு கால அவகாசம் இருந்தது எனவம் நான் உறுதியளிக்கிறேன்.

கேள்விகள் கேட்பதற்கான வாய்ப்பு எனக்கு இருந்தது மேலும் எனது கேள்விகளணைத்தும் எனது திருப்திக்குத் தக்கவாறு பதிலளிக்கப்பட்டிருக்கின்றன.

இந்த ஆய்வில் என் பங்கேற்பு தன்னார்வம் சார்ந்தது எனவும் பங்கேற்பை எப்போது வேண்டுமானாலும் எவ்விதக் காரணமும் அளிக்காமல் என் மருத்துவக் கவனிப்பு அல்லது சட்ட உரிமைகள் பாதிக்கப்படாமல் விலகிக் கொள்ள நான் சுதந்திரமானவர் என்பதை நான் புரிந்து கொள்கிறேன்.

வேண்டிக் கொள்ளப்பட்ட படி ஆய்வு நடைமுறைகளை பின்பற்றவும் மற்றும் மருத்துவர், செவிலிகள் அல்லது மற்ற ஊழிய உறுப்பினர்களுக்கு தேவையான தகவல்களை வழங்கவும் நான் தன்னார்வத்துடன் ஒப்புக் கொள்கிறேன்.

மருத்துவ சோதனையின் ஆய்வு நிறுவனம், நன்னெறிகள் குழு மற்றும் ஒழுங்குமுறை அதிகாரிகள் ஆகியோருக்கு தற்போதைய ஆய்வு சம்பந்தமாகவும் தரவு பாதுகாப்பு அறிக்கையில் குறிப்பிட்டப்படியும் எனது ஆரோக்கியப் பதிவேடுகளைப் பார்வையிடுவதற்கு எனது அனுமதி தேவைப்படாது என்பதை நான் புரிந்து கொள்கிறேன் இந்த அணுகலுக்கு நான் ஒப்புக்கொள்கிறேன் இருந்தாலும் மூன்றாம் நபர்களுக்கு வெளியிடப்படும் அல்லது பிரசுரிக்கப்படும் எந்தவொரு தகவல்களிலும் எனது அடையாளமானது வெளிப்படுத்தப்படாது என்பதை நான் புரிந்து கொள்கிறேன்.

இந்த ஆய்விலிருந்து எழும் எந்தவொரு தரவு அல்லது முடிவுகளின் உபயோகத்தினையும். இது போன்ற உபயோகமானது தரவு பாதுகாப்பு அறிக்கையில் குறிப்பிட்டபடி மட்டுமாக உபயோகிக்கப்படும் பட்சத்தில் அவைகளை நான் தடுக்காமலிருக்க நான் ஒப்புக் கொள்கிறேன்.

மேற்கண்ட ஆய்வில் பங்கெடுக்க நான் ஒப்புக் கொள்கிறேன்.

எனக்காக வைத்துக்கொள்வதற்காக இந்த நோயாளி தகவல் மற்றும் ஒப்புதல் படிவத்தின் ஓர் நகலை நான் பெற்றுக் கொள்கிறேன்.

நோயாளி/ சட்டபூர்வமாக ஏற்றுக் கொள்ளக்கூடிய
பிரதிநிதியின் (எல்ஏஆர்) கையொப்பம் தேதி

(நோயாளி/எல்ஏஆர்)
தாமாகவே
தேதியிட வேண்டும்.

(அல்லது நோயாளி கல்லாதவரானால் பாகுபாடற்ற
சாட்சியின் முன்னிலையில் நோயாளி வாய்மூலமான நோயாளி எண்
ஒப்புதல் கொடுத்திருக்கிறார் என்பதை மற்றும் பெயர்
குறிப்பதற்கான பெருவிரல் ரேகை) நோயாளி பெயர் முதலெழுத்துக்கள்

பிறநத தேதி வயது

சட்டப்பூர்வமாக ஏற்றுக்கொள்ளக்கூடிய
பிரதிநிதி கையொப்பமிட்டால்
நோயாளியுடனான உறவுமுறை

தகவலளிக்கப்பட்ட ஓப்புதல் விவரத்தை நடத்தும்
ஆராய்ச்சியாளர்/ அவரால் நியமிக்கப்பட்டவரின்
பெயர் (அச்சில் அல்லது தட்டச்சில்)

தகவலளிக்கப்பட்ட ஓப்புதல் விவரத்தை நடத்தும் தேதி
ஆராய்ச்சியாளர்/அவரால் நியமிக்கப்பட்டவரின்
கையொப்பம

(ஓப்புதல்
விவரத்தைநடத்தும்
தனிநபர் தாமகவே
தேதயிட வேண்டும்

பாகுபாடற்ற சாட்சியின் கையொப்பம் தேதி
(பொருந்துமானால்)

பாகுபாடற்ற சாட்சியின் பெயர்

பாகுபாடற்ற சாட்சி
தாகமாகவே
தேதியிட வேண்டும்.

Efficacy of Methotrexate in Psoriasis								
					PASI score			
S.NO	Patient ID	Age	Sex	Duration of illness in months	0 month	1 month	3 months	6 months
1	33070	37	M	12	28.4	22.3	14.8	8.4
2	46023	23	F	9	33.8	27.5	13.4	5.9
3	36431	24	M	7	45.7	35.9	21.2	14.6
4	53017	26	M	6	22.6	18.6	6.8	4.9
5	60570	30	F	10	34.1	28.2	9.6	5.8
6	116592	69	M	24	25.4	21.4	6.5	4.2
7	56367	39	M	30	31.4	24.6	5.9	3.2
8	68105	38	M	7	21.5	15.9	7.8	4.7
9	32205	45	M	24	23.4	18.5	6.7	3.9
10	94794	20	F	12	38.6	30.8	10.2	6.9
11	88614	63	M	7	31.9	22.6	9.4	5.2
12	88558	43	M	9	33.2	25.4	8.9	6.8
13	87873	21	M	24	24.7	19.6	6.5	4.6
14	80178	43	M	36	42.6	32.8	10.6	6.8
15	91088	33	M	24	38.9	30.6	11.2	4.6
16	88445	40	M	48	25.2	18.7	10.4	3.4
17	78102	48	M	36	35.7	28.5	12.2	5.8
18	50972	45	F	24	41.6	34.9	11.3	3.9
19	111014	42	M	36	26.9	20.8	9.8	4.6
20	115212	46	M	20	28.5	21.7	7.9	5.2
21	54345	26	M	24	34.3	30.4	9.2	4.7
22	98353	28	M	12	41.7	34.8	10.2	4.9
23	108295	41	F	35	22.7	16.4	6.5	3.9
24	73529	41	M	7	30.4	26.7	8.4	6.9
25	125118	38	M	24	23.8	18.5	5.6	2.5
26	148863	48	F	6	21.3	15.4	4.8	2.1
27	11534	40	F	7	44.6	38.6	8.7	5.3
28	123903	52	M	30	24.9	19.5	6.4	3.9
29	54382	35	F	36	28.6	22.4	9.6	5.7
30	30732	32	M	24	37.8	30.6	8.9	4.7
31	63217	45	F	12	44.2	38.9	9.7	6.3
32	16131	38	F	6	27.3	20.4	8.6	5.4
33	86738	52	F	24	38.6	32.1	10.4	7.6
34	12431	38	F	24	28.2	20.4	9.4	5.3
35	96743	44	M	20	39.2	33.6	10.4	6.4
36	12478	35	M	36	24.9	20.1	11.6	5.6
37	16742	28	F	7	26.5	19.6	8.6	5.8
38	76302	36	F	9	31.5	25.4	11.6	4.7
39	50829	32	F	8	38.7	30.6	13.9	6.5
40	67507	48	F	36	27.6	22.5	13.2	8.4

Efficacy (Pempigus Vulgaris)								
					Pemphigus Area and Activity Score			
S.NO	Patient ID	Age	Sex	Duration of illness in months	0 month	1 month	3 months	6 months
1	72545	48	F	3	34.4	30.2	18.8	12.6
2	67548	61	M	6	28.6	26.2	18.2	10.4
3	83575	32	F	4	25.8	20.4	10.8	8.6
4	72104	21	M	9	18.6	16.2	10.8	7.8
5	54787	31	M	12	38.4	34.2	18.6	11.4
6	62464	31	F	4	22.4	19.2	10.4	8.6
7	42326	40	F	5	24.6	20.4	10.8	8.2
8	52184	35	M	7	21.8	16.8	10.2	6.4
9	48574	47	F	14	40.6	36.4	20.2	12.4
10	53080	47	M	7	38.8	33.8	20.6	11.2
11	21784	29	M	6	21.4	18.2	9.6	6.4
12	21692	37	M	2	16.4	13.2	5.8	6.2
13	42724	45	F	4	19.6	15.8	9.6	7.4
14	22346	30	F	8	42.4	38.6	21.4	13.4
15	52764	35	F	12	35.8	31.8	13.8	10.4
16	34549	28	M	18	28.2	25.8	12.6	9.4
17	38756	30	F	24	34.6	32.8	21.2	12.8
18	48114	33	F	12	31.4	27.6	14.6	10.2
19	51214	54	M	18	29.4	24.8	12.8	8.2
20	54687	40	F	7	33.8	30.4	16.6	9.6

Efficacy (Systemic Sclerosis)								
					Modified Rodnan Skin Score			
S.NO	Patient ID	Age	Sex	Duration of illness in months	0 month	1 month	3 months	6 months
1	66315	55	F	5	13	12	10	7
2	67548	23	F	12	20	18	14	11
3	51040	38	F	24	8	7	6	4
4	50458	20	F	36	28	26	20	14
5	82443	43	F	24	10	9	6	4
6	79201	59	F	6	10	8	6	4
7	84104	40	F	28	10	9	7	5
8	36920	25	F	24	19	17	12	9
9	78624	48	F	18	32	29	21	15
10	81424	50	F	24	18	16	11	8
11	54347	53	F	48	15	13	9	6
12	58236	28	F	12	23	21	17	12
13	58956	45	M	6	12	10	7	5
14	63110	29	F	6	10	9	6	4
15	78108	45	M	36	18	16	12	8
16	80256	35	F	48	24	23	18	11
17	54785	61	F	42	15	14	9	7
18	48481	28	F	12	14	13	9	6
19	43576	30	M	9	10	9	6	4
20	54842	34	F	12	14	12	8	6

Tolerability																				
S.NO	**Patient ID**	**Age**	**Sex**	**Duration of skin disease in months**	**Mucosal ulcer**	**Nausea/vomiting**	**Gastritis**	**Microcytic anemia**	**Macrocytic anemia**	**Leukopenia**	**Weight gain**	**Alopecia**	**Infection**	**Pedal edema**	**Haematuria**	**Menstrual irregularity**	**LFT Elevation**	**Diabetes**	**Hypertension**	**Drug responsible**	**Drug stopped/reduced**
1	33070	37	M	12	p	p	p													Metho	R, T
2	46023	23	F	9								p								Metho	
3	36431	24	M	7	p	p														Metho	R, T
4	53017	26	M	6		p	p	p												Metho	R, T
5	60570	30	F	10																	
6	116592	69	M	24																	
7	56367	39	M	30		p	p													Metho	R, T
8	68105	38	M	7					p											Metho	T
9	32205	45	M	24		p														Metho	T
10	94794	20	F	12								p								Metho	
11	88614	63	M	7																	
12	88558	43	M	9	p	p	p										p			Metho	R, T
13	87873	21	M	24																	
14	80178	43	M	36																	
15	91088	33	M	24		p		p												Metho	R, T
16	88445	40	M	48								p								Metho	
17	78102	48	M	36																	

18	50972	45	F	24	p	p	p												Metho	R, T
19	111014	42	M	36																
20	115212	46	M	20					p										Metho	T
21	54345	26	M	24																
22	98353	28	M	12																
23	108295	41	F	35	p	p	p												Metho	R, T
24	73529	41	M	7								p							Metho	
25	125118	38	M	24																
26	148863	48	F	6				p											Metho	T
27	11534	40	F	7		p													Metho	T
28	123903	52	M	30		p	p					p							Metho	R, T
29	54382	35	F	36																
30	30732	32	M	24																
31	63217	45	F	12	p	p													Metho	T
32	16131	38	F	6																
33	86738	52	F	24		p													Metho	T
34	12431	38	F	24				p											Metho	T
35	96743	44	M	20																
36	12478	35	M	36																
37	16742	28	F	7		p	p												Metho	R, T
38	76302	36	F	9	p														Metho	T
39	50829	32	F	8								p							Metho	
40	67507	48	F	36		p													Metho	T
41	72545	48	F	3		p													Cyclo	T
42	67548	61	M	6		p					p								Cyclo,Dexa	T
43	83575	32	F	4						p			p						Cyclo,Dexa,Aza	T
44	72104	21	M	9		p	p							p				p	Cyclo,Dexa	R,T

45	54787	31	M	12		p		p				p							Cyclo,Dexa,aza	T
46	62464	31	F	4		p													Cyclo	T
47	42326	40	F	5		p	p								p				Cyclo,Dexa,Aza	S,T
48	52184	35	M	7		p						p							Cyclo	T
49	48574	47	F	14										p		p			Cyclo,Dexa	T
50	53080	47	M	7		p				p									Cyclo,Dexa,Aza	T
51	21784	29	M	6		p												p	Cyclo,Dexa	T
52	21692	37	M	2		p												p	Cyclo,Dexa	T
53	42724	45	F	4				p					p						Cyclo,Dexa	T
54	22346	30	F	8		p					p								Cyclo,Dexa,Aza	T
55	52764	35	F	12		p	p												Cyclo,Dexa	T
56	34549	28	M	18	p														Cyclo,Dexa	T
57	38756	30	F	24		p						p							Cyclo	T
58	48114	33	F	12		p					p					p			Cyclo,Dexa	T
59	51214	54	M	18		p													Cyclo	T
60	54687	40	F	7																
61	66315	55	F	5		p								p					Cyclo,Dexa	T
62	67548	23	F	12		p	p				p		p						Cyclo,Dexa	T
63	51040	38	F	24		p		p		p									Cyclo,Dexa	T
64	50458	20	F	36		p	p												Cyclo,Dexa	T
65	82443	43	F	24																
66	79201	59	F	6		p													Cyclo	T
67	84104	40	F	28		p						p							Cyclo	T
68	36920	25	F	24		p													Cyclo,Dexa	T
69	78624	48	F	18																
70	81424	50	F	24		p	p				p								Cyclo,Dexa	T
71	54347	53	F	48		p		p		p			p						Cyclo,Dexa	T

72	58236	28	F	12																
73	58956	45	M	6		p	p												Cyclo,Dexa	T
74	63110	29	F	6										p					Dexa	T
75	78108	45	M	36		p												p	Cyclo,Dexa	T
76	80256	35	F	48		p						p							Cyclo	T
77	54785	61	F	42							p								Cyclo,Dexa	T
78	48481	28	F	12		p	p	p											Cyclo,Dexa	T
79	43576	30	M	9		p													Cyclo	T
80	54842	34	F	12								p							Cyclo	T

P- PRESENT METHO- METHOTREXATE

R-DOSE REDUCTION CYCLO- CYCLOPHOSPHAMIDE

S- DRUG STOPPED AZA- AZATHIOPRINE

T- TREATED DEXA- DEXAMETHASONE

ABBREVIATIONS

ACE	Angiotensin Converting Enzyme
ACTH	Adreno Corticotrophic Hormone
AICAR	Amino Imidazole Carboxamide Ribonucleotide
AIDS	Acquired Immunodeficiency Syndrome
ALL	Acute Lymphoblastic Leukaemias
AP-1	Activator Protein
APCs	Antigen Presenting Cells
ATG	Antithymocyte Globulin
AZT	Azidothymidine
BBB	Blood Brain Barrier
BSA	Body Surface Area
CBC	Complete Blood Count
CBG	Corticosteroid Binding Globulin
CCF	Congestive Cardiac Failure
CD4	Helper T Cells
CD8	Suppressor T cells
CNS	Central Nervous System
CRP	C- Reactive Protein
CTZ	Chemoreceptor Trigger Zone
DCP	Dexamethasone- Cyclophosphamide Pulse Therapy
DHFR	Dihydrofolate Reductase
DLQI	Dermatology Life Quality Index

DM	Diabetes Mellitus
DNA	Deoxy Ribonucleic Acid
EBC	Epstein Barr Virus
ELISA	Enzyme Linked Immunosorbant Assay
ESR	Erythrocyte Sedimentation Rate
FDA	Food and Drug Administration
FKBP	Fk 506 Binding Protein
GIT	Gastro Intestinal Tract
GREs	Glucocorticoid Receptor Elements
HGPRT	Hypoxanthine Guanine Phosphoribosyl Transferase
HIV	Human Immunodeficiency Virus
HLA	Human Leukocyte Antigen
HPA AXIS	Hypothalamo Pituitary Adrenal Axis
HT	Hypertension
IFNs	Interferons
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IIF	Indirect Immunofluorescence
ILs	Interleukins
LFT	Liver Function Test
MED	Minimal Erythema Dose
MHC	Major Histocompatibility Complex
MMF	Mycophenolate Mofetil

MRSS	Modified Rodnan Skin Score
NB-UVB	Narrow Band Ultraviolet-B
NF-κB	Nuclear Factor Kappa- B
NSAIDS	Nonsteroidal Anti-Inflammatory Drugs
PAAS	Pemphigus Area Activity Score
PASI score	Psoriasis Area Severity Index Score
PUVA	Psoralen and Ultraviolet A
PV	Pemphigus Vulgaris
RNA	Ribonucleic acid
SIADH	Syndrome of Inappropriate Anti Diuretic Hormone
TB	Tuberculosis
TEN	Toxic Epidermal Necrolysis
TGF – α	Transforming Growth Factor – α
TH1	T Helper Cell 1
6-TG	6- Thioguanine
TNF – α	Tumour Necrosis Factor – α
TPMT	Thiopurine Methyltransferase Polymorphism
UK	United Kingdom
US	United State
UV	Ultra Violet
WBC	White Blood Cells
XO	Xanthine Oxidase

Ref. No. 6681/E4/3/2013

Govt. Rajaji Hospital,
Madurai.20. Dated: 14. 05.2013

Institutional Review Board / Independent Ethics Committee.
Dr. N. Mohan, M.S., F.I.C.S., F.A.I.S.,
Dean,
Madurai Medical College &
Govt Rajaji Hospital, Madurai 625020.
Convenor

Sub: Establishment-Govt. Rajaji Hospital, Madurai-20-
Ethics committee-Meeting Minutes- for April 2013
Approved list -regarding.

The Ethics Committee meeting of the Govt. Rajaji Hospital, Madurai was held on 29.04.2013, Monday at 10.00 am to 12.00.pm at the Surgery Seminar Hall, Govt. Rajaji Hospital, Madurai. The following members of the committee have attended the meeting.

1.Dr. V. Nagarajan, M.D., D.M (Neuro) Ph: 0452-2629629 Cell.No 9843052029	Professor of Neurology (Retired) D.No.72, Vakkil New Street, Simmakkal, Madurai -1	Chairman
2. Dr.Mohan Prasad , M.S M.Ch Cell.No.9843050822 (Oncology)	Professor & H.O.D of Surgical Oncology(Retired) D.No.72, West Avani Moola Street, Madurai -1	Member Secretary
3. Dr. I. Jeyaraj, M.S., (Anatomy) Cell.No 9566211947	Director & Professor Institute of Anatomy /V.P Madurai Medical College	Member
4. Dr. Parameswari M.D (Pharmacology) Cell.No.9994026056	Director of Pharmacology Madurai Medical College	Member
5. Dr.Moses K.Daniel MD(Gen.Medicine) Cell.No 09842156066	Professor & H.O.D of Medicine Madurai Medical College	Member
6. Dr.D. Soundara Rajan,MS(Gen.Surgery) Cell.No 9842120127	Professor & H.O.D of Surgery Madurai Medical College	Member
7. Dr.Angayarkanni MD(O&G) Cell.No 9443567724	Professor & H.O.D of O&G Madurai Medical College	Member
8. Dr.P.V. Pugalenthi M.S, (Ortho) Cell.No 9443725840	Professor & H.O.D Ortho Madurai Medical College	Member
9. Dr. M. Sundarajan M.S., Mch Cell.No 9994924369 (Neuro Surgery)	Professor (Neuro Surgery) Madurai Medical College	Member
10 Thiru..Pala. .Ramasamy , BA.,B.L., Cell.No 9842165127	Advocate, D.No.72.Palam Station Road, Sellur, Madurai -2	Member
11. Thiru. P.K.M. Chelliah ,B.A Cell.No 9894349599	Businessman, 21 Jawahar Street, Gandhi Nagar, Madurai-20.	Member

The following Project was approved by the committee

Name of P.G.	Course	Name of the Project	Remarks
Dr. S. Yesodha,	PG in MD (Pharmacology) Madurai Medical College, Madurai.	A Study on the efficacy and adverse effects of immunosuppressant drugs in chronic skin disease .	Approved

Please note that the investigator should adhere the following: She/He should get a detailed informed consent from the patients/participants and maintain Confidentially.

1. She/He should carry out the work without detrimental to regular activities as well as without extra expenditure to the institution to Government.
2. She/He should inform the institution Ethical Committee in case of any change of study procedure site and investigation or guide.
3. She/He should not deviate for the area of the work for which applied for Ethical clearance.

She/He should inform the IEC immediately, in case of any adverse events pr Serious adverse reactions.

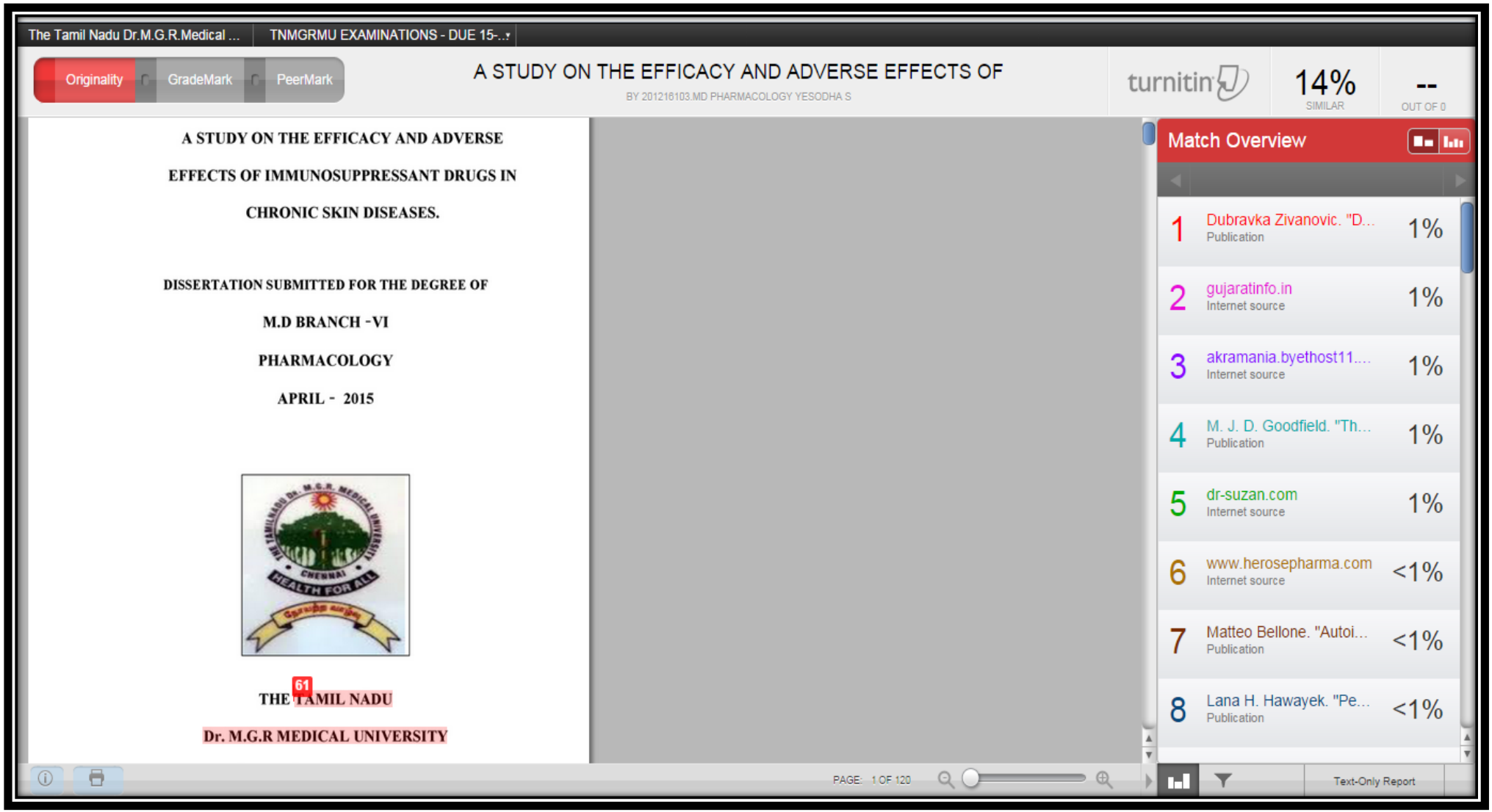
4. She/he should abide to the rules and regulations of the institution.
5. She/He should complete the work within the specific period and apply for if any Extension of time is required She should apply for permission again and do the work.
6. She/He should submit the summary of the work to the Ethical Committee on Completion of the work.
7. She/He should not claim any funds from the institution while doing the word or on completion.
8. She/He should understand that the members of IEC have the right to monitor the work with prior intimation.

Member Secretary **Chairman**

DEAN/Convenor
Govt. Rajaji Hospital,
Madurai- 20.

13/5/13

To
The above Applicant
-thro. Head of the Department concerned.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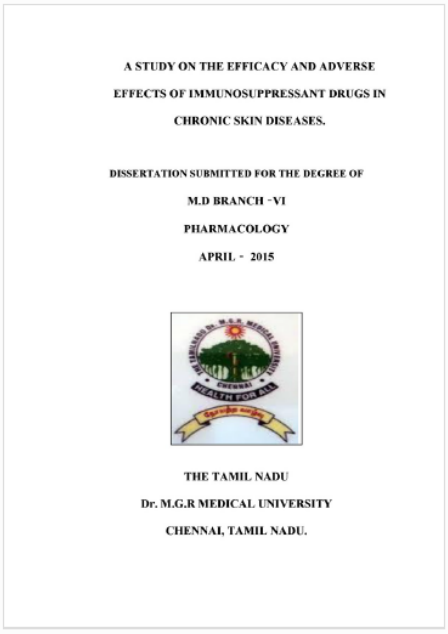

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