ORIGINAL RESEARCH PAPER

Dermatoogy

KEY WORDS:

COMPAARITIVE STUDY OF EFFICACY OF METHOTREXATE VERSUS ACITREETIN IN MODERATE TO SEVERE CHRONIC PLAGUE PSORIASIS

Dr. P Mounika Post Graduate Student, Dermatoogy, Venereology & Laprosy, Osmania Medical College

Dr. Arunasamarth Associate Professor of dermatology dvldep govt mahboobnagar medical college. telanganastate. *Corresponding Author

Dr.G Man Mohan Professor and HOD, Dermatoogy, Venereology & Laprosy, Osmania Medical College

INTRODUCTION

Psoriasis is an immune-mediated polygenic skin disorder. Various environmental triggering factors, e.g. trauma, infections or medications, may elicit disease in predisposed individuals[1]. Psoriasis is found worldwide, affecting approximately 1% to 3% of the population. Men and women are equally affected. Approximately 80% of those affected with psoriasis have mild to moderate disease, with 20% having moderate to severe psoriasis. In patients with moderate to severe psoriasis, there is an increased relative risk for metabolic syndrome and atherosclerotic cardiovascular disease. Psoriasis also has a significant impact on patients' quality of life. [2]

On the basis of the bimodal distribution of the age at onset and inheritance, two types of psoriasis have been discussed. Type I psoriasis approximately 65% of the psoriasis population is associated with onset below the age of 40, a positive family history of psoriasis, a preceding streptococcal sore throat, and guttate lesions. Type II psoriasis (35% of psoriasis patients) appears to be associated with a population with onset after the age of 40 years and with no family history of psoriasis. Type II is not linked to a preceding infectious trigger. [3]

Psoriasis is a complex genetic disease of dysregulated inflammation, although the mechanism of inheritance has not been completely defined. To date, at least 8 chromosomal loci have been identified for which statistically significant evidencefor linkage to psoriasis has been observed (these loci are known as PSORS I-VIII).

Detailed genetic mapping studies demonstrate that the HLA-Cw6 allele, also known as PSORS1, is the major susceptibility gene for psoriasis[4]

In addition, a number of environmental factors play an important role in the pathogenesis of psoriasis including drugs, skin trauma (Koebner's phenomenon), infection, and stress.

The characteristic lesions are sharply demarcated patches varying in size, induration, redness and amount of scales are found symmetrically on the extensor aspects of elbows and knees and lumbosacral region, although almost any part of the body can be affected. The scalp, nails and joints may be involved. In about 20% of the patients with skin psoriasis the nails are affected. Nail changes, present in approximately 50% of the cases, include onycholysis and dystrophy. The nails become pitted and may mimic fungal infection.

Psoriasis is a chronic disease that waxes and wanes during a patient's lifetime, is often modified by treatment initiation and cessation and has few spontaneous remissions.

Various modalities of treatment comprise of topical or systemic medications, photo (chemo) therapy, and an array of biologic agents. Systemic therapies are generally used in patients with severe plaque type disease (>10% body surface area [BSA] or > 10 psoriasis area and severity index[PASI]), generalized pustular psoriasis, psoriatic erythroderma, severe psoriatic arthritis (PsA) and in those who are refractory to topical therapy and phototherapy.

Patients with limited disease but having significant physical or psychosocial disability can also be considered for systemic therapy. It is estimated that about 30% of the patients have moderate to severe disease necessitating systemic therapy[5]

The present study is undertaken to compare the efficacy of methotrexate versus acitretin in moderate to severe psoriasis .Results are evaluated by PASI and compared.

AIMS AND OBJECTIVES

1. To compare the efficacy of methotrexate versus acitretin in 60 patients with moderate to severe psoriasis in the age group of :25-70yrs in both sexes.

REVIEW OF LITERATURE

Psoriasis is a dynamic, genetic, immune mediated, systemic disorder manifesting on the body surface as well as joints in approximately 30 % of patients.

Psoriasis needs a careful clinical evaluation taking into account the extent and form of the disease, quality of life issue, comorbidities such as obesity and full spectrum of metabolic syndrome as well as potential for co-existent psoriaric joint disease.

GENETICS OF PSORIASIS:

The genetic basis of psoriasis is supported by family based investigations; population based epidemiological studies, association studies with human leucocyte antigens (HLAs), genome-wide linkage scans, and candidate gene studies within and outside the major histocompatibility complex (MHC) region[6]

Traditionally, two distinct forms of psoriasis have been noted type 1with early onset (before 40 years of age) likely genetic in origin and type 2 with late onset (older than 40 years),less likely to be genetic .In a clinical & epidemiological study from Spain[7]

Mode of inheritance of psoriasis is complex. Several susceptibility loci for psoriasis vulgaris (*PSORS*) have been identified, but the major genetic determinant of psoriasis is *PSORS1*, which is located within the major histocompatibility complex (MHC) on chromosome 6p. Current data suggest that HLA-Cw6 is the susceptibility allele within *PSORS1*. This association is particularly strong in patients with early onset psoriasis[4] One of the most important features of HLA-C is its capacity to regulate both innate and adaptive responses at the levels of both antigen presentation and natural killer cell

regulation.[8]

With regard to the risk of a child developing psoriasis, a large German survey found that if both parents were affected with psoriasis, the risk for the child developing the disorder was 41%, whereas if one parent were affected, the risk was 14%; if one sibling were affected, the risk was 6%.[9]

IMMUNOPATHOGENESIS:

Pathogenesis of psoriasis is a complex interaction among genetic, immunological, and environmental components. It was previously assumed that Th1 cells played the dominant role in the initiation and maintenance of psoriasis but, in recent years, the view has changed in favour of a Th17 mediated disease. Innate immune cells produce key cytokines (TNF-α, IFN-α, IFN-Y, IL-1β, and IL-6) that activate dendritic cells. Activated dendritic cells present antigens and secrete mediators such as IL-12 and IL-23, leading to the differentiation of Th1 and Th17. IL-23 serves as a key master cytokine regulator. T cells secrete mediators (e.g., IL-17 and IL-22) that activate keratinocytes and induce the production of antimicrobial peptides, proinflammatory cytokines and chemokines. These mediators feed back into the proinflammatory disease cycle and shape the inflammatory infiltrate.[10]

CLINICAL MANIFESTATIONS:

Psoriasis has a significant phenotypic variability, with a range of clinical manifestations. Plaque form psoriasis is the most common, affecting approximately 80% to 90% of patients. Plaque psoriasis manifests as well-defined, sharply demarcated, erythematous plaques varying in size from 1 cm to several centimeters. Table 1 shows morphological variants of psoriasis.

Table 1 Morphological variants of Psoriasis

1. Discoid
2. Elephantine
3. Erythrodermic
4. Flexural
5. Guttate
6. Palmo –plantar
7. Pustular

a) Localised
b) Generalised

Source Menter A et al., Lancet 338,231-238, 1991.

Table 2 : Classification of Psoriasis

1. Mild Psoriasis: Does not affect patient's quality of life .Patients can minimize the impact of disease and may not require treatment.

Treatments have no known serious risks (class 5 topical corticosteroid) Generally less than 5% of BSA is involved with disease.

2. Moderate Psoriasis: Disease does alter the patient's quality of life.

Patient expects therapy will improve quality of life.

Therapies used for moderate disease will have minimal risk (i.e. although these therapies are inconvenient, expensive, time consuming and less than totally effective, they are not recognized as having potential for altering short or long term health.

Generally between 2 and 20% of BSA is involved with the disease.

3. Severe Psoriasis: Disease alters the patient's quality of life.

Disease does not have a satisfactory response to treatments that have minimal risk.

Patients are willing to accept life altering side effects to achieve less less disease or no disease.
Generally more than 10% BSA is involved with disease.
Source :Griffiths CE et al., BR J Dermatol 156,258-262 ,2007.

Table 3: Working definitions of moderate to severe psoriasis

Greater than 20% of BSA involved
Psoriais not responding to topical therapy
Extensive disease not economically feasible to treat topically
Psychologically stressful disease
Gainful employment prevented
Pustular or erythrodermic psoriasis

Scalp psoriasis:

The scalp is one of the most common sites for psoriasis. Unless there is complete confluence, the individual lesions are discrete, in contrast to the less well-defined areas of involvement in seborrheic dermatitis. The lesions of psoriasis often advance onto the periphery of the face, the retroauricular areas and the upper neck.

Nail psoriasis:

Nail involvement has been reported in 10–80% of psoriatic patients. The fingernails are more often affected than the toenails. Psoriasis affects the nail matrix, nail bed and hyponychium. Small parakeratotic foci in the proximal portion of the nail matrix lead to pits in the nails. If the whole nail matrix is involved, a whitish, crumbly, poorly adherent "nail" is seen. Psoriatic changes of the nail bed in the "oil spot" or "oil drop" phenomenon, which reflects exocytosis of leukocytes. Splinter hemorrhages are the result of increased capillary fragility, and subungual hyperkeratosis and distal onycholysis are due to parakeratosis of the distal nail bed.

CO-MORBIDITIES IN PSORIASIS:

Psoriatic patients had a 4-fold increased risk of type 2 diabetes, 3-fold risk of myocardial infarction and life expectancy shortened by 4 years compared to healthy controls. Nearly half of all the psoriasis patients above 65 years of age have at least three co-morbidities. In one study, patients with severe psoriasis were found to die about 3-4 years earlier than patients without psoriasis.

The common comorbidities are enlisted below:

1. Psoriatic arthritis
2. Depression
3. Hypertension
4. Diabetes
5. Obesity
6. Metabolic syndrome
7. Crohn's disease and ulcerative colitis
8. Cardiovascular disease
9. Dyslipidemia
10. Non-alcoholic fatty liver disease
11. Obstructive sleep apnoea
12. Chronic obstructive pulmonary disease

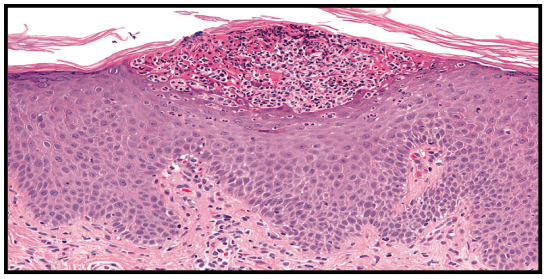
Histopathology:

Initial lesion: In the initial lesion, i.e. a pinhead-sized papule, a superficial perivascular infiltrate of lymphocytes and macrophages is seen in the dermis along with papillary edema and a dilation of capillaries. In acute eruptive guttate lesions, mast cell degranulation is a constant feature. There is mild epidermal acanthosis without parakeratosis and the keratinocytes have a swollen appearance.

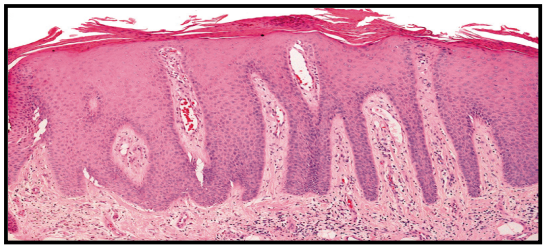
Active lesion: In the dermis, the capillaries are increased in number and length and they have a tortuous appearance. Marked edema is seen, especially at the tops of the papillae. There is a mixed perivascular infiltrate of lymphocytes, macrophages and neutrophils, and lymphocytes and neutrophils have migrated into the epidermis.

The epidermis is acanthotic with focal accumulations of neutrophils and lymphocytes. At these sites, the epidermis is variably spongiotic. Above these foci, the granular layer is absent

and the stratum corneum still contains flattened nuclei (parakeratosis). The accumulation of neutrophils within a spongiotic pustule is referred to as a "spongiform pustule of Kogoj and the accumulation of neutrophil remnants in the stratum corneum, surrounded by parakeratosis, as a microabscess of Munro"



Spogiosiform pustule of kogoj



Hyperpasia of epidermis withs quared off rete ridges
Figure 1 and 2

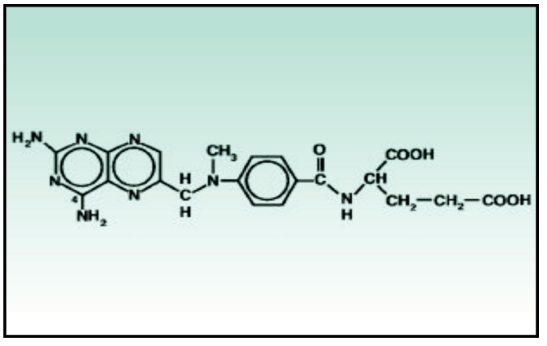
Table 4: Therapeutic Approaches to moderate to severe psoriasis:

Phototherapy : UVB with or without tar and narrow band UVB
Photochemotherapy
Methotrexate
Acitretin
Cyclosporine
Isotretinoin (pustular psoriasis)
Immunomodulatory drugs

METHOTREXATE

Introduction:

Methotrexate (MTX) is an effective agent in the treatment of psoriasis[11], including pustular psoriasis, psoriatic erythroderma, psoriatic arthritis and for extensive chronic plaque psoriasis not controlled by conventional therapy[12–16]. Methotrexate is usually reserved for patients with moderate to severe who have at least 5% of their skin covered with psoriasis who are not responsive to, or eligible for, topical or ultraviolet light treatments (including and PUVA) [12–17]. Methotrexate is an analog of folic acid inhibits cellular proliferation inducing folate coenzyme deficiencies [18].



Strucuture: Figure 3

Mecahanism of action:

MTX inhibits dihydrofolate reductase (DHFR), which is required to produce tetrahydrofolic acid, the active from of folate in humans. Folate is essential for purine and pyrimidine synthesis and thus for the replication of DNA. Methotrexate acts on this enzyme binding to it some 1'000 times more tightly than folate itself resulting in a substantial negative effect on rapidly dividing cells, including cancer cells [19].

However, results of recent *in vitro* studies suggest that MTX causes inhibition of 5-aminoimidazole-4-carboxamide ribonucleotide (AICAR) transformylase leading to accumulation of AICAR, which in turn causes increased tissue concentration of adenosine. Primarily, this increased tissue concentration of adenosine accounts for its anti-inflammatory properties leading to symptom alleviation in psoriasis [20]

A recent study reported that MTX significantly inhibits proliferating lymphoid tissue, particularly T lymphocytes, rather than epidermal cells, i.e., keratinocytes, during low dose once weekly therapy [12, 21]. MTX inhibits T cell activation and suppresses the intercellular adhesion molecule expression by T cells [19]. Interleukin-1 (IL-1), a critical inflammatory cytokine, has some structural similarity to DHFR and it appears to inhibit IL-1 binding to T cell receptors. [22,23]

Pharmacokinetics:

The bioavailability of MTX is generally high (approximately 70%). The onset of action of methotrexate usually occurs within 3–6 weeks of the initiation of therapy. [24] MTX is primarily excreted by the kidneys (~90%), whereas 10%is excreted in bile and feces. The elimination half-life of methotrexate is 3–10 h for the low dose therapy that is used to treat psoriasis. [25–27]

Initiating and monitoring therapy:

1) Before initiating therapy with methotrexate, patients should have a thorough history and physical examination, reviewing alcohol intake, possible exposure to hepatitis B or C, and family history of liver disease.
2) Laboratory tests, including a complete blood count with differential, serum electrolytes, creatinine, liver function tests including albumin and bilirubin, should be obtained for baseline levels. Screening for hepatitis B and C is recommended if risk factors exist as this would contraindicate the use of MTX.
3) Pretreatment liver biopsy should be performed in patients who have abnormal liver function tests, patients with chronic hepatitis, and patients with a history of significant alcohol intake.
4) A chest radiograph is particularly important for patients with underlying pulmonary disease.
5) Additionally, it is very important to discuss appropriate contraception, as methotrexate therapy during pregnancy is known to increase the risk of serious birth defects. [24-28]
6) Due to the well recognized potential for methotrexate to suppress the bone marrow, [29] weekly complete blood count with differential (CBC/diff) is recommended for the first 8 weeks of therapy, followed by every other week for the next 8 weeks of therapy and then every month as long as the patient is taking MTX. [28]
7) Liver function tests should be performed at monthly intervals throughout the course of therapy. If transaminases levels are abnormal or there is an unexplained drop in serum albumin below the normal range, an adjustment of the weekly dose of MTX is advised with repeat blood testing in 2–4 weeks. [28,30] If liver function tests remain elevated, a liver biopsy is indicated. The extent of fibrosis on liver biopsy dictates whether MTX can be continued. If a patient refuses to undergo a liver biopsy, it is prudent to discontinue MTX. [28,30]
8) More frequent monitoring of both laboratory studies and liver histology should be performed if other hepatotoxic medications are used along with methotrexate.

Dosage/administration:

MTX is administered in an intermittent low-dose once weekly

regimen. Administration can be oral, intramuscular or subcutaneous. Although there are no established maximum or minimum dosages of MTX, weekly dosages usually range from 7.5 to 25 mg given orally or parenterally.[28,31]

Folic acid, given 1 mg daily 6 of 7 days of the week, protects against some of the common side effects seen with low-dose MTX including stomatitis, hepatotoxicity and gastrointestinal intolerance.[32]

Side effects:

60–90% of patients treated with MTX develop minor adverse reactions, including gastrointestinal distress (nausea, vomiting, diarrhea, or anorexia), stomatitis, headaches, and fatigue.[33]

Severe potentially life threatening toxicities of methotrexate include myelosuppression, hepatotoxicity, and pulmonary damage. These toxicities occur at a significantly higher frequency in patients treated with high dose methotrexate used to treat malignancy, but can also occur with chronic low dose weekly therapy used to treat inflammatory diseases such as psoriasis. Up to 30% of patients treated with chronic low dose MTX for more than 5 years need to discontinue therapy due to the development of serious toxicities.[33]

Myelosuppression:

With low dose weekly therapy, pancytopenia may be observed. This is more likely in the elderly and with overdose or drug interactions. Furthermore, renal function impairment results in sustained serum levels of MTX that can result in bone marrow toxicity.[29,34] In case of acute hematological toxicity or accidental overdose with MTX, it is necessary to immediately prescribe its antidote intravenously, namely folinic acid, citrovorum factor or leucovorin at a similar dose to that of methotrexate

Hepatotoxicity:

Hepatotoxicity manifests as fibrosis of increasing severity, which may culminate in cirrhosis. Recently it has been found out that methotrexate-induced liver damage is clinically and histopathologically similar to NAFLD, and there is a greater risk of progression to NASH with higher cumulative doses or in the presence of risk factors. Updated guidelines on liver biopsy to assess MTX induced toxicity recommend that psoriasis patients should be divided into two groups based on the presence of risk factors for liver injur.[31]

Low risk psoriasis patients need not undergo baseline biopsy and liver function tests should be done at regular intervals. Liver biopsy is done at a cumulative dose of 3.5–4 g or earlier if there are more than five persistent elevations in five of nine aspartate aminotransferase (AST) levels over a 12-month period or if there is a decline in serum albumin below the normal range with normal nutritional status in the setting of well-controlled disease.[31]

In the high risk patients, baseline liver biopsy is done after giving MTX for 2–6 months and repeat biopsy is done after every 1–1.5 g of cumulative dose.[31]

Recently, many direct and indirect markers of liver function have come up for the monitoring.[35 ,36] Indirect markers include aspartate aminotransferase (AST), alanine aminotransferase (ALT), Y glutamyltranspeptidase, hyaluronic acid, apolipoprotein A1, bilirubin, haptogloblin, cholesterol, platelets, and prothrombin time. Direct markers of liver function include collagen IV, collagen VI, tissue inhibitor of metalloproteinase-1 (TIMP-1), laminin, human cartilage glycoprotein 39, tenascin, undulin, matrix metalloproteinase-2 (MMP-2), and amino terminal of procollagen III peptide PIIINP).

Two recent studies have found estimation of pro-collagen 3 N-terminal peptide (PIIINP) as a useful marker of liver damage and that liver biopsies could be entirely avoided if PIIINP levels remained stable.[37,38] .PIIINP assay has a limitation that it is not organ specific and measures ongoing fibrogenesis only.

Pulmonary toxicity:

Methotrexate pneumonitis is rarely seen in patients receiving low dose weekly treatment for psoriasis but it does occur and it can be fatal[39].

Infections and malignancies:

Since methotrexate works as an immunosuppressive agent by inhibiting lymphocyte function, rare reports of infection and malignancy are not unexpected[40]. However, a clear association between MTX use and malignancy has not been confirmed[41–43]. While there have been many reports of lymphoproliferative disease occurring in rheumatoid arthritis patients treated with methotrexate[44] , only rarely has lymphoproliferative disease been associated with methotrexate treatment in patients with psoriasis[45] . High dose methotrexate therapy is considered a risk factor for the development of non-melanoma skin cancer, particularly squamous cell carcinoma(SCC). However, no studies confirm an increased incidence of SCC in psoriasis patients receiving low-dose methotrexate monotherapy. Conversely, therapy with psoralen and ultraviolet A irradiation (PUVA) significantly increases the overall risk of SCC[46–48].

Contraindications

MTX should not be given to anyone with a history of hypersensitivity to MTX, cytopenia, active liver disease, alcoholism, active infection, or pulmonary hypersensitivity.

Renal insufficiency reduces the clearance of MTX and its active metabolites thus increasing the risk of toxicity.

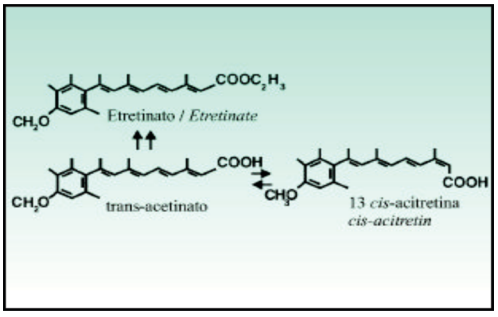
Pregnancy is an absolute contraindication for treatment with MTX because MTX is teratogenic and multiple congenital deformities have been reported including hydrocephalus, cleft palate, skeletal abnormalities, and abnormal facial features[49,50].

Adequate contraception (for male as well as female patients) is absolutely necessary while taking MTX. In males, methotrexate can cause reversible oligospermia and defective sperm[51].Women should not become pregnant for 1 month and men should avoid fathering children for 3 months following cessation of methotrexate therapy[52, 53] . Women should not breastfeed while taking MTX.

Patients taking MTX should not receive live virus vaccines.

ACITRETIN

Acitretin, the active metabolite of etretinate, is the most commonly used oral retinoid for psoriasis.



Structure: Figure 4

Mechanism of action:

It is hypothesized that acitretin is metabolized to molecules that bind to RARs. Transactivation of RAR elements (RAREs) and indirect effects by down-regulating certain genes that do not have direct effects on gene transcription mediated through retinoic acid response RARE, thus inducing negative

effect on gene transcription leading to anti-proliferative and anti-inflammatory effects. [54]

Pharmcokinetics:
After oral administration, its absorption may vary between individuals (from 36 to 95%) [56] .The metabolism of acitretin occurs mainly in the liver.

Etretinate is the prodrug of acitretin, which is its active metabolite, presenting under the isomeric form with trans and cis interconvertible metabolites, both teratogenic[55,56] . Although it has a better pharmacokinetic profile (only slightly lipophilic and with a half-life from two to four days), small amounts of acitretin can be converted into etretinate, which is 50 times more lipophilic and has a slower elimination half-life (from 80 to 175 days). [55,56]

The reaction is enhanced, both in vivo and in vitro by ethanol [57] .This has created concern that birth defects might result if acitretin-treated women inadvertently ingest alcohol, which is commonly used in cough syrup, over-the-counter medications and cooking ingredients. Because of this knowledge, the recommended period for contraception after acitretin therapy has been lengthened from 2 months to 2 years. [57]

Initiation & monitoring therapy:
1) In the evaluation prior to therapeutics, it is mandatory to dose hepatic enzymes (GOT, GPT, alkaline phosphatase, bilirubin, gamma-glutamyl transferase), total cholesterol and triglycerides, besides glucose, urea, creatinine, complete blood count and urine summary. [56,58]
2) When intending to initiate long-term therapy, the bone status evaluation is suggested and, in children and adolescents, bone age and growth parameters. These procedures should be repeated annually. [56,58,59]
3) The dosage of hepatic enzymes and the lipid profile should be repeated at the end of two weeks of treatment, then monthly for the following three months and after this, at every three months.
4) Women who could potentially become pregnant should sign a consent term and be counseled to use a contraceptive method for three years after discharge. It is mandatory to perform a pregnancy test (ß-HCG) prior to treatment and then on a monthly basis.
5) Neither women nor men using acitretin should donate blood during the treatment and for a further three years afterwards.

Dosage :
Optimal dose range for monotherapy is 25 to 50 mg/day. [60] Improvement occurs gradually, requiring up to 3-6 months for peak response. Higher doses (50-75 mg/day) result in more rapid and possibly more complete response but are associated with significantly increased side effects.

Teratogenicity:
Acitretin is an embryotoxic and teratogenic drug (category X), the main malformations are: congenital anomalies of the CNS (hydrocephaly and microcephaly); ocular malformations; small or absent ears; facial dysmorphism; cleft palate; bone alterations with defects in the members; cardiovascular anomalies; thymic defects; parathyroid hormone deficiency; and mental retardation [56,59,62] . In men, acitretin does not alter the spermatogenesis.

Mucocutaneous side effects:
The most frequent, but are treatable, dose-dependent and reversible with a decrease in the dose or suspension of the treatment. They include: cheilitis (82 to 96%), dry mouth, dry nose, epistaxis, dry eyes, intolerance to contact lenses, blepharoconjunctivitis, xerosis, pruritus, photosensitivity, palmoplantar desquamation and also of the digital pulps, cutaneous desquamation, cutaneous fragility, adherent skin, difficulty in cicatrization, colonization of the skin by S. aureus, fragile nails, ungual dystrophy, pyogenic periungual granulomas, alopecia, alteration of the hair texture, vaginitis, urethritis and rectal bleeding . [56,59,61]

Hyperlipidemia:
In most of the reported cases, the alterations reverted following a reduction in the dosage, combined with dietary alterations or treatment with hypolipemiant drugs. The triglyceride levels should not exceed 800 mg/dl due to the risk of pancreatitis and eruptive exanthoma. [56,59] Lipid abnormalities may be managed by reducing the dose of acitretin, making appropriate dietary changes, or by means of lipid-lowering medications as needed. Lipid levels normalize in most patients after discontinuation of retinoid therapy

Hepatotoxicty:
Most important laboratorial alterations are rises of the GOT and GPT hepatic enzymes (from five to 33%).

Use of acitretin may cause transient and reversible elevations in serum liver enzymes. Severe hepatotoxic reactions resulting from retinoid use are rare and idiosyncratic. It is recommended to do routine monitoring of liver function more frequently in alcoholics, diabetics, obese individuals; and if possible, concurrent use of hepatotoxic agents should be avoided. [63]

Pancreatitis:
Increases of serum triglycerides to levels associated with pancreatitis are not common, although a case of fatal fulminant pancreatitis has occurred. Patients at high risk include those with diabetes mellitus, obesity, increased alcohol intake, or a family history of hypertriglyceridemia. [61,64]

Pseudotumor cerebri:
Pseudotumor cerebri, or benign intracranial hypertension, has occurred in very rare cases with use of systemic retinoids including acitretin. This effect has been associated with concurrent tetracycline or minocycline administration. [65]

Hyperostosis:
Studies examining effects of retinoids (etretinate and acitretin) on bone have shown that retinoid effects on bone, if present at all, likely involve worsening of pre-existing skeletal overgrowth rather than de novo changes. Induction of new bony abnormalities occurred in fewer than 1% of patients. [65]

PATIENTS AND METHODS
In the present study 60 clinically diagnosed cases of moderate to severe psoriasis attending Dermatology, Venerology Leprosy OPD at Osmania General Hospital were enrolled.

Study period: December 2013 to August 2015
This is a Prospective interventional study

Inclusion criteria:
1) Patients with erythema , redness and scaling with moderate to severe clinical presentation
2) Age group of 25-70 yrs.
3) Both males and females were included.
3) No prior treatment with methotrexate /acitretin.
4) PASI > 10 /BSA > 20

Exclusion criteria:
1) Taking other treatments for the disease,
2) Suffering from anemia, thrombocytopenia, leukemia,
3) Active infection (e.g. tuberculosis, septicemia),
4) Peptic ulcer disease and alcoholism
5) Patients with hepatic and renal damage, cardiovascular disease, abnormal serum lipid profile.
6) Pregnant women and lactating mothers were also excluded.

The patients satisfying the inclusion and exclusion criterion as mentioned are taken for the study after an informed written consent.

Patients were divided into groups , Group A was given METHOTREXATE and Group B was given ACITRETIN .

Following parameters are noted on entry into the study
1. Detailed history
2. Examination –systemic and cutaneous
3. Investigations

Details included:
Informed written consent was taken from all patients
1. Demographic profile (age and gender),
2. Duration of disease
3. Provoking factors both topical and oral medications
4. Associated medical illness
5. Site of involvement
6. Size of plaque
7. Severity of plaque measured by Psoriasis Area and Severity Index (PASI) score before starting the treatment and at the end of treatment.

The primary endpoint was the proportion of patients achieving ≥75% improvement in Psoriasis Area and Severity Index (PASI 75) after 12 weeks of therapy.

TABLE -5 PASI SCORE WORKSHEET

Plaque characteristic	Lesion score	Head	Upper Limbs	Trunk	Lower Limbs
Erythema	0 = None 1 = Slight 2 = Moderate 3 = Severe 4 = Very severe				
Induration/Thickness					
Scaling					
Add 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)					
Add together each of the scores for each body region to give the final PASI Score.					

PASI Score = ☐

Laboratory investigations prior to intrervention:
1. Complete blood picture with platelet count
2. Erythrocyte sedimentation rate
3. Random blood sugar
4. Liver function tests
5. Renal function tests
6. Serum lipid profile
7. Skin biopsy.

OBSERVATION AND RESULTS

Table – 6 PASI before Methotrexate in Group A

PASI	10-19.9	20 -29.9	30 -39.9	40 -49.9
No of members	8	13	8	1

In group A before Methotrexate ,out of 30 patients ,8 are having PASI in the range of 10 -19.9,13 members are in the range of 20-29.9, 8 in the range of 30-39.9 and one member is having PASI of 40 -49.9.

Chart -1 PASI before Methotrexate in Group A

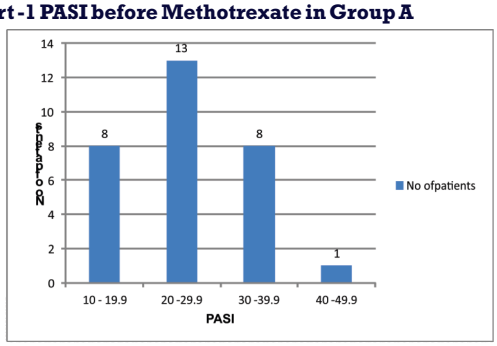


Table-7 PASI After Methotrexate in Group A

PASI	0-4.9	5 -9.9	10 -14.9	15-19.9
No of members	21	4	4	1

In Group A , after Methotrexate 21 members are having PASI in the range of 0-4.9,4 each in the range of 5-9.9 & 10 -14.9 and one member is having a PASI in the range of 15-19.9

Chart -2 PASI After Methotrexate in Group A

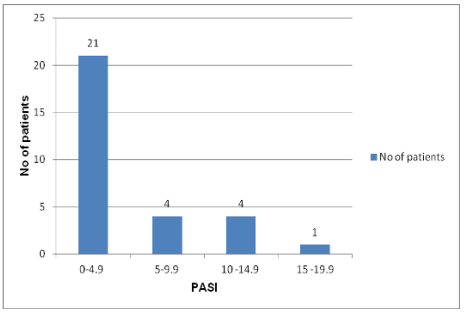


Table-8 Gender wise distribution of PASI Before Methotrexate

PASI	10-19.9	20 -29.9	30 -39.9	40 -49.9
Male	6	6	7	1
Female	1	8	1	0

In A group of 30 members before Methotrexate , in the PASI range of 10-19.9 (6M,1 F),in the range of 20-29.9 (6M, 8F) ,30-39.9 (7M,1F),40 -49.9 (1M)

Chart-3 Gender wise distribution of PASI Before Methotrexate

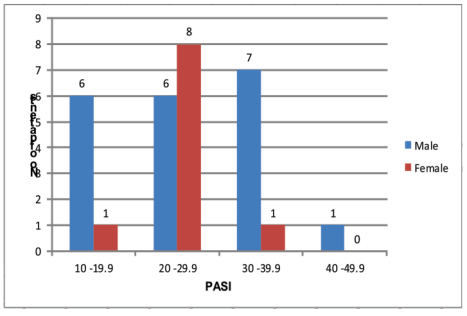


Table-9 Genderwise distribution of PASI After Methotrexate

PASI	0-4.9	5-9.9	10 -14.9	15 -19.9
Male	15	1	2	2
Female	6	3	1	0

In group A of 30 members after Methotrexate, PASi in the range of 0-4.9 (15M ,6F) ,in the range of 5-9.9 (1M,3F),10 -14.9 (2M,1F),15 -19.9 (2M)

Chart-4 Genderwise distribution of PASI After Methotrexate

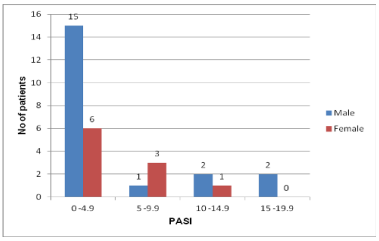


Table -10 MeanPASI before and after treatment with duration in Group A

Duration	Mean PASI Before	Mean PASI After
<2years	22	3.4
2- <4years	26.5	5.6
4 - <6years	22	4.3
6 – 8 years	33	9.1

Chart -5 Mean PASI before and after treatment with duration in Group A

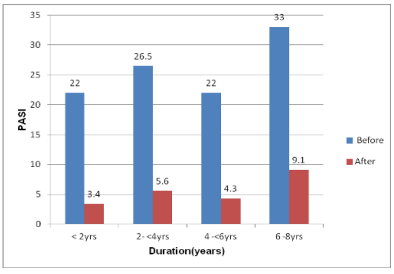


Table -11 Methotrexate side effects

Side effects of Methotrexate	GI symptoms	Abnormal LFT	Haematological S/E	Others
Percentage	30%	15%	8%	1%

Group A of 30 members 30% had GI symptoms, 15% had Abnormal LFT, 8% had haematological abnormalities and other side effects in 1%.

Chart -6 Methotrexate side effects

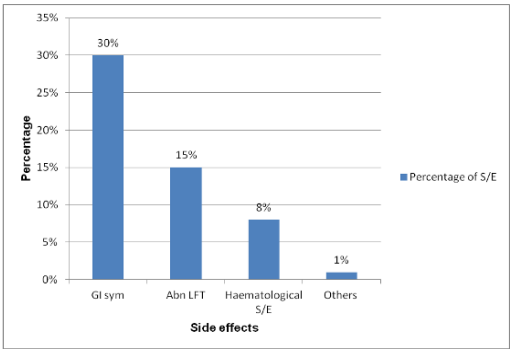
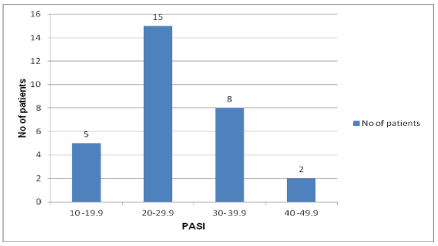


Table -12 PASI Before Acitretin in Group B

PASI	10-19.9	20 -29.9	30 -39.9	40 -49.9
No of members	5	15	8	2

IIn group B before Acitretin ,out of 30 patients ,5 are having PASI in the range of 10 -19.9,15 members are in the range of 20-29.9,8 in the range of 30-39.9 and two members are having PASI of 40 -49.9.

Chart -7 PASI Before Acitretin in Group B



able-13 PASI After Acitretin in Group B

PASI	0-4.9	5 -9.9	10 -14.9	15-19.9
No of members	14	6	9	1

In Group B ,after Acitretin 14 members are having PASI in the range of 0-4.9, 6 in the range of 5-9.9 ,9 in 10 -14.9 range and one member is having a PASI in the range of 15-19.9

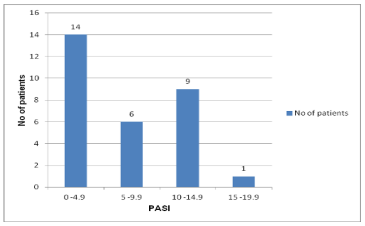


Table-14 Gender wise distribution of PASI before Acitretin

PASI	10-19.9	20 -29.9	30 -39.9	40 -49.9
Male	3	10	4	1
Female	2	5	4	1

In group B of 30 members before Acitretin in the PASI range of 10-19.9 (3M,2 F),in the range of 20-29.9 (10M, 5F) ,30-39.9 (4M,4F),40 -49.9 (1M,1F)

Chart-9 Gender wise distribution of PASI before Acitretin

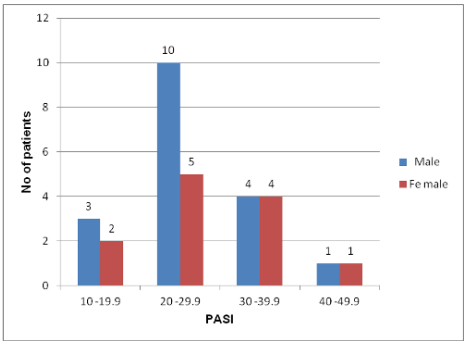


Table-15 Gender wise distribution of PASI after Acitretin

PASI	0-4.9	5-9.9	10 -14.9	15 -19.9
Male	10	4	4	0
Female	4	2	5	1

In group B of 30 members after Acitretin ,PASI in the range of 0-4.9(10M ,4F) ,in the range of 5-9.9 (4M,2F),10 -14.9 (4M,5F),15 -19.9 (1F)

Chart-10 Gender wise distribution of PASI after Acitretin

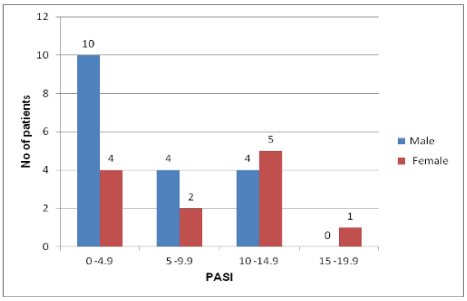


Table -16 Mean PASI before and after treatment with duration in Group B

Duration	Mean PASI Before	Mean PASI After
<2years	22	6.2
2- <4years	26	6.5
4 - <6years	26.2	7.5
6 – 8 years	26.8	8.5

Chart -11 Mean PASI before and after treatment with duration in Group B

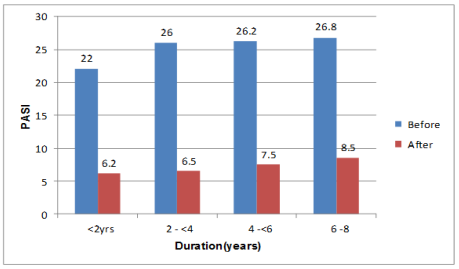


Table 17 :Acitretin Side Effects

Side effects of Acitretin	Mucocutaneous S/E	Lipid Profile abn	Hepatotoxicity	Others
Percentage	60%	30%	13%	1%

Group B of 30 members 60% had Mucocutaneous side effects,30% had Abnormal lipid profile,13% had elevated liver enzymes and other side effects in 1%.

Chart -12 Acitretin Side Effects

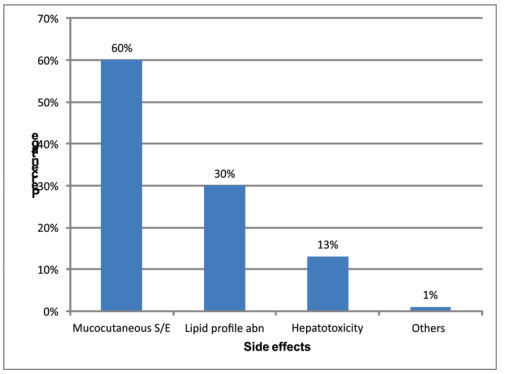


Table 18 Comorbidities Of Psoriasis

Comorbidity	Diabetes	Hypertension	Obesity	Metabolic syndrome
No of cases	14	12	10	5

Out of 60 patients of pisorasis,14 had diabetes, hypertension (12),obesity (10),& metabolic syndrome(5)

Chart 13 Comorbidities Of Psoriasis

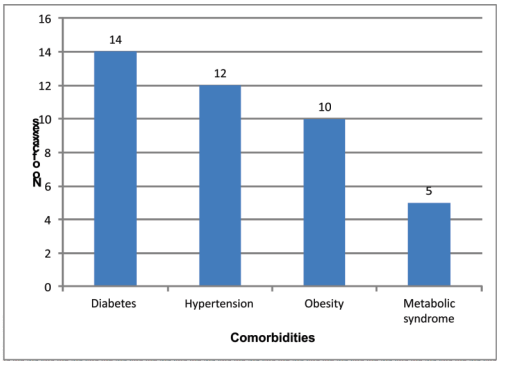


Table -19 PASI 75% after 12 weeks of therapy

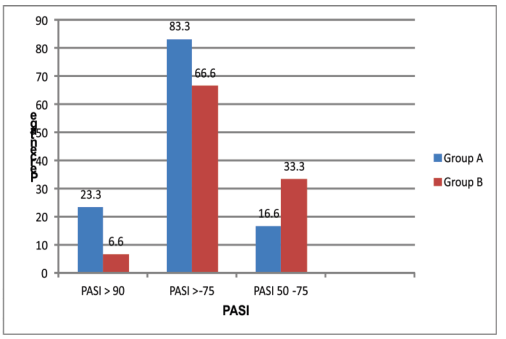
Group	PASI >90	PSAI >-75	PASI <75
A	23.3%	83.3%	16.6%
B	6.6%	66.6%	33.3%
Total	29.9%	149.6%	49.9%

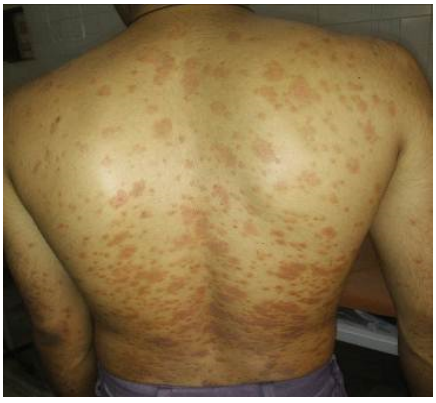
In Group A ,patients with PASI >90%(23.3%), PASI reduction of ≥75%(83.3%)and PASI <75% (16.6%)

In Group B ,patients with PASI >90%(6.6%), PASI reduction of ≥ 75%(66.6%)and PASI <75% (33.3%)

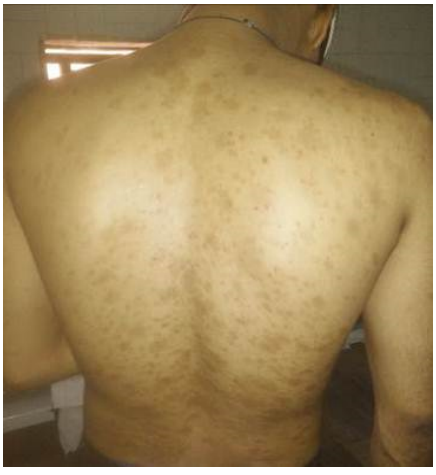
The p value is 0.076 for PASI ≥ 75, the difference between the efficacy of two drugs is not significant.

Chart -14 PASI 75% after 12 weeks of therapy

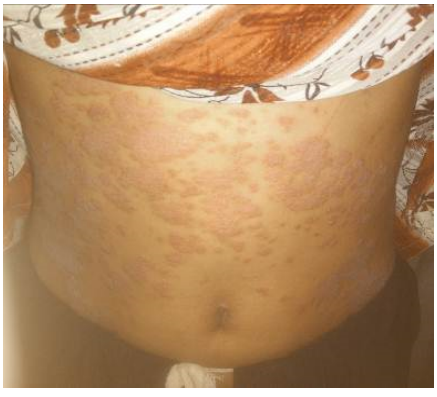




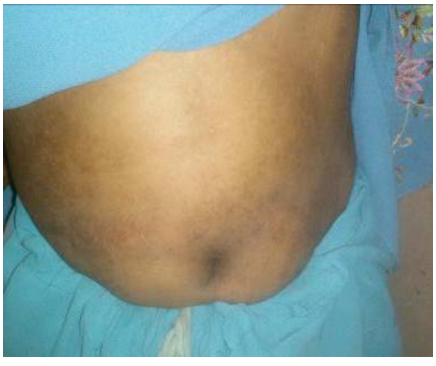
Before methotrexate
Figure No 5



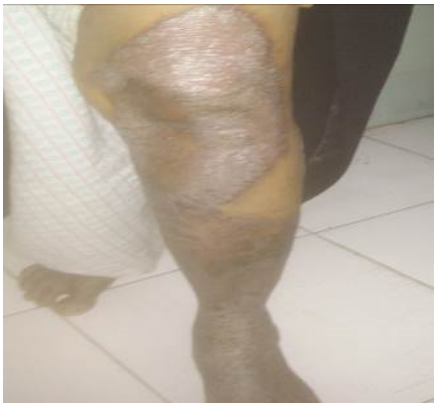
After methotrexate
Figure No 6



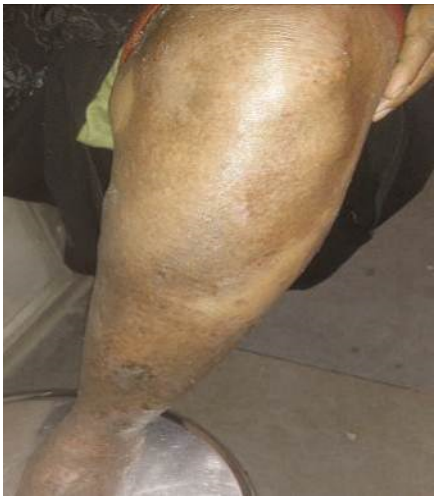
Before methotrexate
Figure No 7



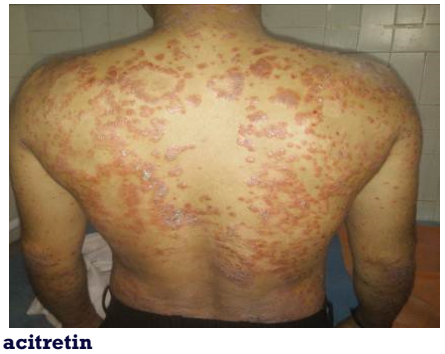
After methotrexate
Figure No 8



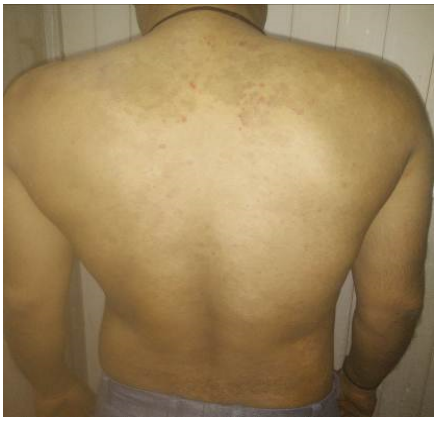
Before acitretin
Figure No 9



After acitretin
Figure No 10



Before acitretin
Figure No 11



Before acitretin
Figure No 11

Histopathology Before treatment

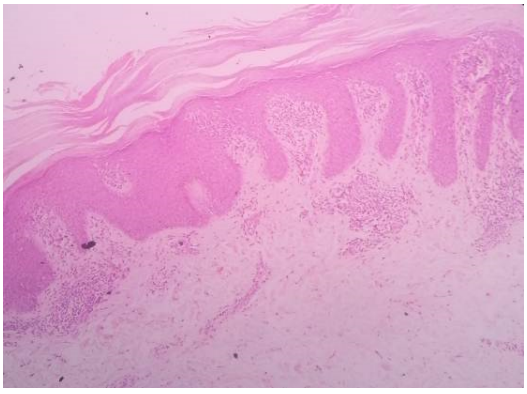


Figure No 13

Epidermis shows hyperkeratosis, parakeratosis, acanthosis, with broad rete ridges and intra epidermal micro munro abcesses; dermis shows mononuclear cell inflammatory cell collections around blood vessels.

Histopathology After treatment

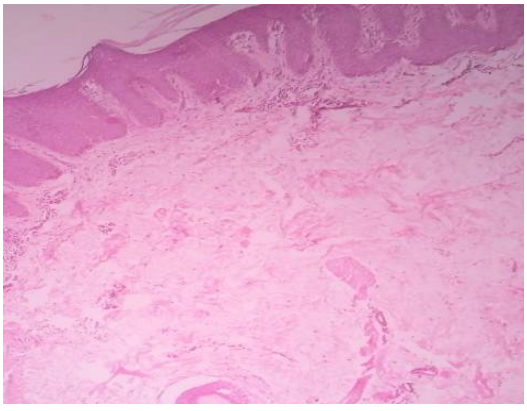


Figure No 14

Epidermal hyperkeratosis decreased, there is shortening of rete ridges and disappearance of mononuclear inflammatory infiltrate .

DISCUSSION

Psoriasis affects both the genders with some predilection for male but the result vary according to sampling methodology and most studies exclude females [66-68] . Although women may have an early onset, the age of onset varies across reported studies and bimodal distribution has been reported between 16-22 and 57-60 years of age.

However, the disease has no phenotypic difference in either sex.

Out of 60 patients comprised 38 male and 22 females aged 25 -65 years (mean 41+/-SD11.5) years and their demographic profile in both the groups were comparable between them and with the reported studies [68-72] .

The fewer number of female patients in this study is perhaps for the simple reason of their exclusion during child-bearing age from such studies, small sample size or perhaps that fewer women seek medical treatment at early stage of their disease.

The duration of psoriaisis in the study ranges from 3months to 8 years with mean of 3.47yrs(+/- 2.36 SD)

The objective of treatment of psoriasis is to gain initial and rapid control of disease process, maintain long-term remission and improve quality of life [73,74]

Although there is no cure for psoriasis but several treatments can minimize the disease and some can also induce remission of months to years [75]

The therapeutical algorithm for severe psoriasis vulgaris now includes photo(chemo-) therapy in combination with topical substances, oral fumaric acid esters, retinoids (in combination with phototherapy or topical substances), methotrexate, cylosporine and the new biologics.

Topical therapy is considered as the first line therapy for psoriasis, however many patients do not respond or have extensive disease. Systemic therapy is required for these patients, which include photochemotherapy, conventional systemic, and more recently biological agents. [73,76,77]

The current management of severe psoriasis is based on the principles of rotational therapy, which stresses frequent alternations in treatment approaches in order to reduce the cumulative risk of side effects [73]

The choice of treatment is influenced by short-term as well as long-term considerations, including the severity of the disease, the effectiveness of a given medication and its side effects, the patient's quality of life and the ease of treatment. According to the guidelines for the treatment of psoriasis, which are based on the 1997 review, UVB should be tried first, and if it proves to be ineffective, it should be followed in order by PUVA, methotrexate, acitretin, and finally, cyclosporine [78,79,]

In latest consensus guidelines for the management of plaque psoriasis [80] published in 2012 it was proposed that methotrexate may be used as a first-line systemic drug for plaque psoriasis and compared with cyclosporine, has a more modest effect, but can be used continuously for years or decades.

In this randomized trial of two frequently used systemic treatments in patients with moderate-to-severe chronic plaque psoriasis, In Group A, patients with PASI >90% were 23.3%, PASI reduction of ≥75% were 83.3%and PASI <75% were 16.6% In Group B ,patients with PASI >90% were 6.6% ,PASI reduction of ≥75% were 66.6% and PASI <75% were 33.3%.

The p value is 0.076 for PASI ≥75 ,indicating the difference between efficacy of two drugs is not significant .

Both drugs for moderate-to-severe psoriasis are readily available, and there is ample evidence of their effectiveness from placebo-controlled studies and uncontrolled studies.

METHOTREXATE

The mean pretreatment PASI score in our Group-A patients was 25±SD7.5 and at the end of the study 23.3% patients achieved almost complete remission, 83.3% patients achieved PASI 75 and 16.6% patients achieved PASI <75.The mean percentage reduction in PASI score of 81.65 ± SD 11.67 after 12 weeks of treatment.

Kumar et al [81] reviewed 244 psoriatic patients treated with weekly oral methotrexate from 1981 to 2000 and observed more than 75% improvement in 88% patients in 8.5±5.1 weeks .Comparable with the present study.

Haustein et al [82] in a 26-year retrospective study had 157 patients with extensive plaque psoriasis or erythrodermic, pustular and arthropathic forms treated with low-dose methotrexate (15-20 mg/week) for long-term periods. The effect of methotrexate was good in 76% patients, moderate in 18% patients and poor in 6% patients and only 20% of cases

discontinued the therapy due to side effects. Comparable with present study.

Abhinav C et al [83] Weekly methotrexate versus daily isotretinoin to treat moderate-to-severe chronic plaque psoriasis: a comparative study in which pretreatment PASI was 12.21±5.24 and at the end of the study 35.71% patients achieved almost complete remission, 64.29%patients achieved PASI 75 and 85.71% patients achieved PASI 50.The above results were lower compared to the present study.

In a study done by Opmeer BC et al.[84], base line PASI score were 13.4 ± 3.6 and at the end of 16 week were 5.0± 4.5.The above results were lower compared to the present study.

Heydendael et al [85] observed complete remission (>90% reduction in baseline PASI score) in their 40% patients and partial remission (>75 % reduction in their baseline PASI score) in 60% patients. The above results were lower compared to the present study.

Sabiqa Haider et al [86]Out of 73 patients there were 45 (61.6%) males and 28 (38.4%) females. The mean ±SD age was 40.0±12.6 years. The mean baseline PASI score showed clear and comparable improvement from a mean ± SD PASI score of 14.8±4.2 to 4.9±4.3.Twenty nine (40%) patients had an almost complete remission during the 8 weeks of treatment. Partial remission was achieved in 44 (60%) patients. The clearance time for psoriasis ranged from 5-7 weeks (mean 6±0.89 weeks). The above results were lower compared to the present study, probably because of short duration of this study.

Weinstein et al [66] and **Sandhu et al** [69] observed more than 75% improvement **Griffiths et al** [87] suggested that methotrexate reduces the severity of psoriasis by at least 50% in at least 75% of patients.

Table 20 Comparision of efficacy of methotrexate with arious studies

Studty name	Present study	Kumar et al	Haustein et al	Abhinav C et al	Opmeer BC et al	Heydendael et al	Sabiqa Haider et al
%of cases achieved PASI 75	83.3%	88%	76%	64.29%	62.7%	60%	60%

Side effects

Nine (30%) patients in Group-A experienced methotrexate induced nausea, vomiting, retching and/or anorexia and were managed with antiemetics. Mild abnormality of liver enzymes were found in 6(20%) patients and haematolological abnormalities in 2(7%) patients which did not warrant discontinuation of therapy.

In a study done dy BL Masuria et al [88] , Methotrexate : Side effects and the role of folic acid supplementation in psoriasis - Twenty-three out of 50 (46%) patients experienced some kind of side effects with methotrexate e therapy. In 15 (30%) of them, side effects were gastrointestinal in nature ,4 (8%) had non-gastrointestinal side effects and 4 (8%) had side effects of both GI and non-GI nature. Majority of these patients had taken conventional antiemetics and H2 blockers for methotrexate related G I symptoms in past with little or no benefit. Once folic acid was supplemented, the side effects reported with methotrexate pulse were reduced to minimum and patients were able to accept therapy much better. The above side effects were comparable with the present study.

In study done by Abhinav C et la [83] (57.14%) patients experienced methotrexate induced nausea, vomiting, retching and/or anorexia from first month to end of the study period and were managed with antiemetics. Mild abnormality of liver enzymes and thrombocytopenia in one patient each at the end of 8 weeks warranted its discontinuation. However, the patient developing thrombocytopenia had already achieved PASI 75 before discontinuation of methotrexate. The above side effects were higher compared to the present study.

Table 21 Comparision of side effects of Methotrexate with various studies

Study name	Present Study	BL Masuria et al	Abhinav C et al
Side effects			
GI sym	30%	30%	57.4%
Other S/E	27%	16%	Mild

Acitretin

The mean pretreatment PASI score in our Group-B patients was 26±SD 6.55 and at the end of the study 6.6% patients achieved almost complete remission, 66.6% patients achieved PASI 75 and 33.3% achieved PASI <75 . The mean percentage reduction in PASI score of 75.2 ± SD 12.25 after 12 weeks of treatment .

Murray HE et al. [89] A 12-month treatment of severe psoriasis with acitretin – The authors of study enrolled 63 patients in which efficacy was assessed following 12 months of treatment with acitretin reported that, of the 37 patients who completed the study, 89% had a PASI 50 response and 78.4% a PASI 75 response. The above results were higher compared to the present study probably because of long duration of study

Kragballe KJansen CTGeiger JM et al. [90] A double-blind, randomized study compared the therapeutic effectiveness and the tolerability of acitretin (n = 127) and etretinate (n = 41) in psoriasis. Patients were treated with 40 mg daily for the first 4 weeks and with an individually adjusted dose for the subsequent 8 weeks. The average daily doses of acitretin (0.54 mg/kg/day) and etretinate (0.65 mg/kg/day) were similar. The PASI (Psoriasis Area and Severity Index) scores improved in parallel in the 2 treatment groups. At the completion of the study, the PASI score improvement was 75.8% for acitretin and 70.8% for etretinate. The above results were higher compared to the present study probably because of high initial dose used.

A.Lassus,J.M. et al [91] Treatment of severe psoriasis with etretin :A study that examined efficacy at 8 weeks in patients who received an initial dose of 10, 25, or 50mg of acitretin reported a mean reduction in PASI of 61%, 79%, and 86%, respectively, in the 3 treatment groups as compared to 30% in the placebo group. The above results were higher compared to the present study.

Alessandro Borghi et al [92] :Low-dose Acitretin in Treatment of Plaque-type Psoriasis: Descriptive Study of Efficacy and Safety The efficacy and safety of acitretin was evaluated retrospectively in a cohort of 46 patients with moderate to severe plaque psoriasis (Psoriasis Area and Severity Index (PASI) range 10–42). Efficacy measures were: (i) PASI75 (75% improvement) and PASI 50 between 10 and 16 weeks; and (ii) PASI 75 even after 16 weeks of treatment. At weeks 10–16, PASI 75 and were achieved by 47.8% and 87% of the patients, respectively. Overall, 67.3% reached PASI 75. Adverse events occurred in 18 patients (39.1%); among these, 4 (8.7%) discontinued acitretin. The above results were lower compared to the present study.

S. Dogra*, et al [93] **:** Efficacy and safety of acitretin in three fixed doses of 25, 35 and 50 mg in adult patients with severe plaque type psoriasis: a randomized, double blind, parallel group, dose ranging study**,** results After 12 weeks of therapy, the percentage reduction in the PASI score was 54%, 76% and 54% in acitretin 25, 35 and 50 mg/day group respectively. PASI

75 was achieved in 47%, 69% and 53% patients in acitretin 25, 35 and 50 mg/day groups respectively. The above results were lower compared to the present study

Gollnick H et al [94] Acitretin versus etretinate in psoriasis, 175 patients with severe psoriasis of different types were treated with 10, 25, or 50 mg acitretin and compared with patients receiving 50 mg etretinate over a period of 8 weeks in a randomized, double-blind multicenter study in the Federal Republic of Germany. A greater than 50% PSI score improvement was seen in 50% of patients treated with 10 mg acitretin, 40.5% with 25 mg acitretin, 53.8% 50 with mg acitretin, and 61.1% with 50 mg etretinate. The above results were lower compared to the present study probably because of short duration of treatment.

van de Kerkhof PC et al [95] The effect of addition of calcipotriol ointment (50 micrograms/g) to acitretin therapy in psoriasis. Patients were randomized to receive calcipotriol or placebo. All patients were treated with a starting dose of 20 mg acitretin per day and doses were adjusted at 2-weekly intervals with increments of 10 mg per day up to a maximum of 70 mg per day. Seventy-six patients were randomized to treatment with calcipotriol 50 micrograms/g ointment twice daily and 59 patients to treatment with the vehicle only twice daily. Clearance or marked improvement was achieved by 67% of the patients in the calcipotriol group and by 41% of the patients in the placebo group (P = 0.006). The above results were lower compared to present the study.

Olsen EAWeed WWMeyer CJCobo *LM* [96] :A double-blind, placebo-controlled trial of acitretin for the treatment of psoriasis. All 15 patients then completed at least 8 weeks with 25 to 75 mg acitretin daily, with a moderate change in erythema, scaling, and induration (mean 28% to 37% improvement) but with minimal change in the percentage of body surface area involved. Prolonged treatment (≥20 weeks) with acitretin resulted in further significant improvement and a 44% reduction of involved surface area from baseline. The above results were lower compared to the present study .

Table 22 Comparision of efficacy of Acitretin with various studies

Study name	Present study	Murray HE et al	Kragballe et al	A.Lassus et al	Alessandro Borghi	S.Dogra et al	Gollnick H et al	van de Kerkhof PC et al
%of cases achieved PASI 75	66.6%	78.4%	75.8%	79%	47.8%	47%	40.5%	41%

Side effects

18 (60%) patients in Group-A experienced acitretin induced mucocutaneous effects and were managed with emollients . Mild abnormality of lipid profile were found in 9(30%) patients and liver enzyme abnormalities in 4(13%) patients which did not warrant discontinuation of therapy.

Balkrishna P Nikam et al [97] In an analysis of 176 patients receiving acitretin in clinical trials at the standard recommended doses of 25 to 50 mg/day, cheilitis occurred in approximately 60 to 75%, skin peeling in 25 to 50%, rhinitis in 20 to 30%, dry skin in 15 to 25% and hair loss in 10 to 25%. Other effects such as sticky skin, rigors, itchiness and dry mouth were less common, occurring in fewer than 25% of patients, even those receiving the highest doses .The above side effects were comparable to the present study.

Katz HI et al [61] **.** Acitretin in poriasis: An overview of adverse effects.

Gupta AK et al. [64] Side-effect profile of acitretin therapy in psoriasis. In 525 patients receiving acitretin therapy in clinical trials with doses ranging from 10 to 75 mg/day, increases in triglyceride levels occurred in 66% and increases in total cholesterol occurred in 33% of patients. In addition, levels of HDL decreased in approximately 40% of patients. Lipid levels normalize in most patients after discontinuation of retinoid therapy. The above side effects were higher compared to the study probably because of higher range of dose used .

MD Henry H. Roenigk Jr et al [63] Effects of acitretin on the liver. treated 128 adults (with chronic, stable psoriasis) with oral acitretin (25–75 mg/day) for four 6-month intervals in a prospective, open-label, 2-year multicenter study. Liver biopsies were performed before and after study completion (2 years).

Eighty-three available pairs of pretreatment and post treatment liver biopsies demonstrated no change in 49 patients (59%), improvement in 20 (24%), and worsening in 14 (17%). Of these 14 patients with decrements in biopsy status, most changes were mild. The above side effects were higher compared to the present study probably because of higher dose and long duration of study.

Table 23 Comparision of side effects of Acitretin with various studies

Studty name	Present study	Balkrishna P et al	Ratz HI, Gupta AK et al	MD HenryH. Roenigk Jr et al
Side effects			_	
Chelitis	60%	60-75%	Trigycerides -66%	_
Lipid profile	30%	_	Cholosterol-33%	_
Hepatoxicity	13%	_	_	24%

Comorbities of psoriasis

Of the study population which consisted of 60 psoriasis patients, we identified 14 (23.3%)diabetics which correlated with the incidence rates as observed in studies by **Shapiro et al.** (30.5%) [98]

The incidence of hypertension was 12(20%) . This correlated with similar incidence rates as studied by Y.Wu et al.(24.4%). These rates were comparatively higher than those observed by **Niemann et al**(11.9%)(99) and very low compared to those seen in study by **Shapiro et al.**(51.5%) [98]

Out of 60 cases with psoriasis, 5(8.3%) satisfied the criteria for metabolic syndrome .

Among the 60 cases , 16.6 %(10) were diagnosed to be obese .These rates were comparatively slightly higher than **Niemann et al** [99] (13.1%) and **Shapiro et al**(13.3%) [98]

Table 24 Comparision of Comorbidities of Psoriais with various studies

Comorbidity	Present study	Shapiro et al	Niemann et al
Diabetes	23.3%	30.5%	_
Hypertension	20%	51.5%	11.9%
Obesity	16.6%	13.3%	13.1%

In the present study, clinical and laboratory parameters were studied to compare efficacy of methotrxate versus acitretin in moderate to severe chronic plaque psoriasis.

These parameters are as follows:

1. Age of patients,
2. Duration of the disease
3. Gender of the patients,
4. Presence of personal history predisposing /aggravating factors like smoking ,drinking and stress
5. Presence of any comorbities

6. BSA and PASI
7. Laboratory investigations to identify any derangement of liver function, lipid profile and haematological abnormalities.

SUMMARY AND CONCLUSION

A total number of 60 consecutive cases of moderate to severe chronic plaque psoriais reporting to the Dermatology Venereology Leprology department of Osmania Genereal hospital were studied.

22 of them were females and 38 were males.

The age group of cases were in the range of 25-65years .

1) Cases were allocated into two groups ,Group A were given Methotrexate and GroupB Acitretin
2) Pretreatment investigations and PASI score were done .
3) Cases were given drugs and followed up for 12 weeks along with necessary investigations
4) PASI was calculated every 4 weeks intrerval.
5) Limitations of the study are: Its an un-blinded study , small sample size
6) At the end of 12 weeks , PASI 75 was achieved in Group A by 83.3 % patients and Group B by 66.6 % cases.
7) Statistical analysis (p value) of these patients did not show a significant difference between efficacy in patients treated with methotrexate and acitretin in chronic plaque psoriasis.
8) There is paucity of studies comparing the efficacy of Methotrexate versus Acitretin.
9) In agreement with present study observations, other studies had comparable results with Methotrexate and Acitretin.
10) Oral methotrexate is more effective , cheaper and leads to a faster clearance of the disease as compared to acitretin.
11) Monotherapy with acitretin for plaque-type psoriasis is often less successful; however, its use in combination with other therapies is highly effective in treating this form of the disease. As monotherapy, acitretin has been shown to be effective in treating erythrodermic psoriasis and retinoid is the choice of drug in generalized pustular psoriasis.

REFERENCES

1. Nestlé FO, Kaplan DH, Barker J. Psoriasis. N Engl J Med. 2009;361:496–509.
2. Christophers E. Psoriasis—epidemiology and clinical spectrum. Clin Exp Dermatol. 2001;26:314–20.
3. Gudjonsson JE, Karason A, Antonsdottir AA, Runarsdottir EH, Gulcher JR, et al. HLA-Cw6-positive and HLA-Cw6-negative patients with Psoriasis vulgaris have distinct clinical features. J Invest Dermatol. 2002;118(2):362-365.
4. Nair, R.P., Stuart, P.E., Nistor, I., Hiremagalore, R. et al. Sequence and haplotype analysis supports HLA-C as the psoriasis susceptibility 1 gene. Am J Hum Genet. 2006;78:827–851
5. Liem WH, Mccullough JL, Weinstein GD. Effectiveness of topical therapy for psoriasis: Results of a national survey. Cutis 1995;55:306-10.
6. Rahman P, Gladman DD, Schentag C, Petronis A. Excessive paternal transmission in psoriatic arthritis. Arthritis Rheum. 1999;42:1228–31.
7. Capon F ,Novelli G,Semperini S ,et al.Searching for Psoriais susceptibility genes in Italy :genome scan and evidence for a new locus to chromosome 1q. J Invest Dermatol1999;112;32-35
8. Balato A, Unutmaz D, Gaspari AA. Natural killer T cells: an unconventional T-cell subset with diverse effector and regulatory functions. J Invest Dermatol. 2009;129:1628-1642
9. Farber EM, Nall ML. The natural history of 5600 patients.Dermatologica. 1974;148:1–18.
10. DiMeglio P, Perera GK, Nestle FO. The multitasking organ: recent insights into skin immune function. Immunity. 2011 Dec23;35(6):857-869.
11. Ryan TJ, Vickers HR, Salem SN, Callender ST, Badenoch J (1964) The treatment of psoriasis with folic acid antagonist. Br J Dermatol 76: 555–564
12. Boffa M, Chalmers R (1996) Methotrexate for psoriasis. Clin Exp Dermatol 21: 399–408
13. Ryan TJ, Baker H (1969) Systemic corticosteroids and folic acid antagonists in the treatment of generalized pustular psoriasis: evaluation and prognosis based on the study of 104 cases. Br J Dermatol 81: 134–145
14. Rosenbaum MM, Roenigk HH Jr, (1984) Treatment of generalized pustular psoriasis with etretinate and methotrexate. J Am Acad Dermatol 102: 357–361
15. Black RL, O'Brien WM, Van Scott EJ, Auerbach R, Eisen AZ, Bunim JJ (1964) Methotrexate therapy in psoriatic arthritis. J Am Med Assoc 189: 743–747
16. Espinoza LR, Zakraoui L, Espinoza CG, Gutierrez F, Jara LJ, Silveira LH, et al (1992) Psoriatic arthritis: clinical response and side effects to methotrexate therapy. J Rheumatol 19: 872–877
17. Bright R (1999) Methotrexate in the treatment of psoriasis. Cutis 64: 332–334
18. Cronstein BN (1996) Molecular therapeutics: Methotrexate and its mechanism of action. Arthritis Rheum 39: 1951-1960
19. Goodsell DS (1999) The molecular perspective: Methotrexate. The Oncologist 4: 430–441
20. Johnston A, Gudjonsson JE, Sigmundsdottir H, Ludviksson BR, Valdimarsson H. The anti-inflammatory action of methotrexate is not mediated by lymphocyte apoptosis, but by the suppression of activation and adhesion molecules. Clin Immunol 2005;114:154-63.
21. Jeffes EWB, McCullough JL, Pittelkow MR, McCormick A, Almanzor J, Liu G, et al (1995) Methotrexate therapy of psoriasis: differential sensitivity of proliferating lymphoid and epithelial cells to the cytotoxic and growth-inhibitory effects of methotrexate. J Invest Dermatol 104: 183–188
22. Miller LC, Cohen FE, Orencole SF, Schaller JG, Savage N, Dinarello CA (1988) Interleukin-1 beta is structurally related to dihydrofolate reductase: effects of methotrexate on IL-1. Lymphokine Res 7: 272A
23. Brody M, Bohm I, Bauer R (1993) Mechanism of action of methotrexate: experimental evidence that methotrexate blocks the binding of interleukin 1 beta to the interleukin 1 receptor on target cells. Eur J Chem Clin Biochem 31: 667–674
24. Olsen EA (1991) The pharmacology of methotrexate. J Am Acad Dermatol 25: 306–618
25. Jolivet J, Cowan KH, Curt GA, Clendeninn NJ, Chabner BA (1983) The pharmacology and clinical use of methotrexate. N Engl J Med 309: 1094–1104
26. Thomson Micromedex Healthcare Series. The Drugpoint summary for methotrexate. Available at http://www.micromedex.com (accessed 23 January 2007)
27. Huffman DH, Wan SH, Azarnoff DL, Hoogstraten B (1973) Pharmacokinetics of methotrexate. Clin Pharmacol Ther 14: 572–579
28. Roenigk HH Jr, Auerbach R, Maibach H, Weinstein G, Lebwohl M (1998) Methotrexate in psoriasis: Consensus conference. J Am Acad Dermatol 38: 478–485
29. Singh Y, Aggarwal A, Misra R, Agarwal V (2007) Low-dose methotrexate-induced pancytopenia. Clin Rheumatol 26: 84–87
30. Kremer HM, Phelps CT, Lightfoot RW Jr, Willkens RF, Furst DE, Williams HJ, et al (1994) Methotrexate for rheumatoid arthritis. Suggested guidelines for monitoring liver toxicity. American College of Rheumatology. Arthritis Rheum 37: 316–328
31. Menter A, Korman NJ, Elmets CA, Feldman SR, Gelfand JM, Gordon KB, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis: Section 4. Guidelines of care for the management and treatment of psoriasis with traditional systemic agents. J Am Acad Dermatol 2009;61:451-85.
32. Strober BE, Menon K (2005) Folate supplementation during methotrexate therapy for patients with psoriasis. J Am Acad Dermatol 53: 652–659
33. Goodman TA, Polisson RP (1994) Methotrexate: Adverse reactions and major toxicities. Rheum Dis Clin North Am 20: 513–528
34. Gutierrez-Urena S, Molina JF, Garcia CO, Cuellar ML, Espinoza LR (1996) Pancytopenia secondary to methotrexate therapy in rheumatoid arthritis. Arthritis Rheum 39: 272
35. Barker J, Horn EJ, Lebwohl M, Warren RB, Nast A, Rosenberg W, et al. Assessment and management of methotrexate hepatotoxicity in psoriasis patients: Report from a consensus conference to evaluate current practice and identify key questions toward optimizing methotrexate use in the clinic. J Eur Acad Dermatol Venereol 2011;25:758-64.
36. Smith JO, Sterling RK. Systematic review: Non-invasive methods of fibrosis analysis in chronic hepatitis C. Aliment Pharmacol Ther 2009;30:557-76.
37. Chalmers RJ, Kirby B, Smith A, Burrows P, Little R, Horan M, et al. Replacement of routine liver biopsy by procollagen III aminopeptide for monitoring patients with psoriasis receiving long-term methotrexate: A multicentre audit and health economic analysis. Br J Dermatol 2005;152:444-50.
38. Maurice PD, Maddox AJ, Green CA, Tatnall F, Schofield JK, Stott DJ. Monitoring patients on methotrexate: Hepatic fibrosis not seen in patients with normal serum assays of aminoterminal peptide of type III procollagen. Br J Dermatol 2005;152:451-8.
39. Phillips TJ, Jones DH, Baker H (1987) Pulmonary complications following methotrexate therapy. J Am Acad Dermatol 16: 373–375
40. Shiroky JB, Frost A, Skelton JD, Hoegert DG, Newkirk MM, Neville C (1991) Complications of immunosuppression associated with weekly low dose methotrexate. J Rheumatol 18: 1172–1175
41. Weinblatt ME (1996) Methotrexate in rheumatoid arthritis: toxicity issues. Br J Rheumatol 35: 403–405
42. Kamel OW, van de Rijn M, Weiss LM, Del Zoppo GJ, Hench PK, Robbins BA, et la(1993) Brief report: Reversible lymphomas associated with Epstein-Barr virus occurring during methotrexate therapy for rheumatoid arthritis and dermatomyositis. N Engl J Med 328: 1317–1321
43. Bologna C, Picot MC, Jorgensen C, Viu P, Verdier R, Sany J (1997) Study of 8 cases of cancer in 426 rheumatoid arthritis patients treated with methotrexate. Ann Rheum Dis 56: 97–102
44. McClure SL, Valentine J, Gordon KB (2002) Comparative tolerability of systemic treatments for plaque-type psoriasis. Drug Saf 25: 913–927
45. Paul C, Le Tourneau A, Cayuela JM, Devidas A, Robert C, Molinie V, et al (1997) Epstein-Barr virus-associated lymphoproliferative disease during methotrexate therapy for psoriasis. Arch Dermatol 133: 867–871
46. Stern RS, Laird N (1994) The carcinogenic risk of treatments for severe Lindskov R (1983) Skin carcinomas and treatment with photochemotherapy (PUVA). Acta Derm Venereol 63: 223–226
48. Stern RS, Zierler S, Parrish JA (1982) Methotrexate used for psoriasis and the risk of noncutaneousor cutaneous malignancy. Cancer 50: 869–872
49. Buckley LM, Bullaboy CA, Leichtman L, Marquez M (1997) Multiple congenital anomalies associated\ with weekly low dose methotrexate treatment of the mother. Arthritis Rheum 40: 971–973
50. Milunsky A, Graef JW, Gaynor MF Jr, (1968) Methotrexate induces congenital malformations. J Pediatr 72: 790–795
51. Georgouras KE, Zagarella SS, Cains GD, Brown PJ (1997) Systemic treatment of severe psoriasis. Australas J Dermatol 38: 171–180
52. Jeffes EW 3rd, Weinstein GD (1995) Methotrexate and other chemotherapeutic agents used to treat psoriasis. Dermatol Clin 13: 875–890
53. Wolverton SE (1991) Systemic drug therapy for psoriasis: the most critical issues. Arch Dermatol 127: 565–568
54. Chandraratna RA. Rational design of receptor- selective retinoids. J Am Acad Dermatol 1998;39:S124-8.
55. Saurat J-H. Retinoids and psoriasis: Novel issues in retinoid pharmacology

and implications for psoriasis treatment J Am Acad Dermatol 1999; 41:S2-6.
56. Berbis P. Acitrétine Ann Dermatol Venereol 2001; 128:737-45.
57. Koo J, Nguyen Q, Gambla C. Advances in psoriasis therapy. Adv Dermatol 1997;12:47-72.
58. Lebwohl M, Ali S. Treatment of psoriasis. Part 2. Systemic therapies J Am Acad Dermatol2001;45:649-61.
59. Brecher AR, Orlow SJ. Oral retinoid therapy for dermatologic conditions in children and adolescents. J Am Acad Dermatol 2003; 49:178-82.
60. Ling MR. Acitretin: Optimal dosing strategies. J Am Acad Dermatol 1999;41:S13-7.
61. Katz HI, Waalen J, Leach EE. Acitretin in psoriasis: An overview of adverse effects J Am Acad Dermatol 1999;41:S7-12.
62. Yamauchi PS, Rizk D, Kormeili T et al. Current systemic therapies for psoriasis: Where are we now? J Am Acad Dermatol 2003;49:S66-77.
63. Roenigk Jr. HH, Callen JP, Guzzo CA, Katz HI, Lowe N, et al. Effects of acitretin on the liver. J Am Acad Dermatol 1999;41:584-8
64. Gupta AK, Goldfarb MT, Ellis CN, Voorhees JJ. Side-effect profile of acitretin therapy in psoriasis. J Am Acad Dermatol 1989;20:1088-93.
65. Van Dooren-Greebe RJ, Lemmens JA, De Boo T, Hangx NM, Kuijpers AL, van de Kerkhof PC. Prolonged treatment with oral retinoids in adults: No influence on the frequency and severity of spinal abnormalities. Br J Dermatol 1996;134:71-6.
66. Weinstein GD, Frost P. Methotrexate for psoriasis: a new therapeutic schedule. Arch 1971:103:33-Dermatol.8.
67. van Doore-Greebe RJ, Kuijpers ALA, Mulder J, Boo TD, van de Kerkhof PCM Methotrexate revisited. effects of long-term treatment in psoriasis. Br J Dermatol. 1994;130:204-10.
68. Ranjan N, Sharma NL, Shanker V, Mahajan VK, Tegta GR. Methotrexate versus hydroxycarbamide (hydroxyurea) as a weekly dose to treat moderate-to-severe chronic plaque psoriasis: A comparative study. J Dermatolog Treat. 2007;18:295-300.
69. Sandhu K, Kaur I, Kumar B, Saraswat A. Efficacy and safety of cyclosporine versus methotrexate in severe psoriasis: a study from north India. Indian J Dermatol. 2003;30:458-63.
70. Flystorm I, Stenberg B, Svensson A. Methotrexate vs cyclosporin in psoriasis: effectiveness, quality of life and safety. A randomised controlled trial. Br J Dermatol. 2008;158:116-21.
71. Akhyani M, Chams-Davatchi C, Hemami MR, Fateh S. Efficacy and safety of mycophenolate mofetil vs. methotrexate for the treatment of chronic plaque psoriasis. J Eur Acad Dermatol Venereol. 2010;24:1447–51.
72. Arani SF, Neumann H, Hop WCJ and Thio HB. Fumarates vs. methotrexate in moderate to severe chronic plaque psoriasis: a multicentre prospective randomized controlled clinical trial. Br J Dermatol. 2011;164:855-61
73. Mashhood AA, Imran A. Pathogenesis of psoriasis. J Pak Assoc Derma. 2005;15(1):42–54.
74. Shehzad T, Dar NR, Zakria M. Efficacy of concomitant use of PUVA and methotrexate in disease clearance time in plaque type Psoriasis. J Pak Med Assoc. 2004;54(9):453–455.
75. Witman PM. Topical therapies for localized psoriasis. Mayo Clin. 2001;76:943–949.
76. Rich P, Sigurgeirsson B, Thaci D, Ortonne JP, Paul C, Schopf R, et al. Secukinumab induction and maintenance therapy in moderate-to-severe plaque psoriasis: a randomized, double-blind, placebo-controlled, phase II regimen-finding study. Br J Dermatol. 2013;168(2):402–411. doi: 10.1111/bjd.12112. [PubMed]
77. McClure SL, Valentine J, Gordon KB. Comparative tolerability of systemic treatments for plaque type psoriasis. Drug Saf. 2002;25(13):913–927.
78. Naldi L. Epidemiology of psoriasis. Curr Drug Targets Inflamm Allergy. 2004;3(2):121–128.
79. Asim SA, Ahmed S, Najam-us-Sehar Psoralen-ultraviolet a treatment with Psoralen-ultraviolet B therapy in the treatment of psoriasis. Pak J Med Sci. 2013;29(3):758–761. doi: 10.12669/pjms.293.2622.
80. Hsu S, Papp KA, Lebwohl MG, Bagel J, Blauvelt A, Duffin KC, et al. Consensus guidelines for the management of plaque psoriasis. Arch Dermatol. 2012;148(1).
81. Kumar B, Saraswat A, Kaur I. Short-term methotrexate therapy in psoriasis: a study of 197 patients. Int J Dermatol. 2002;41:444-8.
82. Haustein UF, Rytter M. Methotrexate in psoriasis: 26 years' experience with low-dose long-term treatment. J Eur Acad Dermatol Venereol 2000; 14:382–8.
83. Abhinav C, Mahajan VK, Mehta Ks, Chauhan PS, Gupta M, Rawat M. Weekly methotrexate versus daily isotretinoin to treat moderate-to-severe chronic plaque psoriasis: a comparative study . Our Dermatol Online. 2015;6(4):392-398.
84. Opmeer BC, Heydendael VM, De Borgie CA, Spuls PI, Bossuyt PM, Bos JD, et al. Costs of treatment in patients with moderate to severe plaque psoriasis: economic analysis in a randomized controlled comparison of methotrexate and cyclosporine. Arch Dermatol. 2004;140(6):685–690.doi:10.1001/archderm. 140.6.685.
85. Heydendael VM, Spuls PI, Opmeer BC, de Borgie CA, Reitsma JB, Goldschmidt WF, et al. Methotrexate versus cyclosporine in moderate-to-severe chronic plaque psoriasis. N Engl J Med 2003;349:658-65
86. Sabiqa Haider, Zarnaz Wahid, Najam-us-Saher, and Farzana Riaz Efficacy of Methotrexate in patients with plaque type psoriasisPak J Med Sci. 2014 Sep-Oct; 30(5): 1050–1053.
87. Griffiths CEM, Clark CM, Chalmers RJG, Li Wan Po A, Williams HC. A systematic review of treatments for severe psoriasis. HealthTechnol Assess. 2000;4:1-133.
88. BL Masuria, A Mittal, LK Gupta, M Sharma, N Bansal , Methotrexate : Side effects and the role of folic acid supplementation in psoriasis – Indian journal of dermatology and venerology Year : 1997 | Volume : 63 | Issue : 4 | Page : 219-222
89. Murray HE, Anhalt AW, Lessard R et al. A 12-month treatment of severe psoriasis with acitretin – results of a Canadian open multicenter study. J Am Acad Dermatol 1991; 24:598–602
90. Kragballe KJansen CTGeiger JM et al. A double-blind comparison of acitretin and etretinate in the treatment of severe psoriasis: results of a Nordic multicentre study. Acta Derm Venereol 1989;69 (1) 35- 40
91. A. Lassus, J.M. Geiger, M. Nyblom, T. Virrankoski, M. Kaartamaa, L. Ingervo Treatment of severe psoriasis with etretin (RO 10-1670) Br. J. Dermatol., 117 (1987), pp. 333-341
92. Borghi A, Corazza M, Bertoldi AM, Caroppo F, Virgili Low-dose Acitretin in Treatment of Plaque-type Psoriasis:.Acta Derm Venereol. 2015 Mar;95(3):332-69
93. S. Dogra, A. Jain and A.J. Kanwar Efficacy and safety of acitretin in three fixed doses of 25, 35 and 50 mg in adult patients with severe plaque type psoriasis: a randomized, double blind, parallel group, dose ranging study, Journal of the European Academy of Dermatology and Venereology Volume 27, Issue 3, pages e305–e311, March 2013
94. Gollnick H, Bauer R, Brindley C, Orfanos CE, Plewig G, Wokalek H, et al. Acitretin versus etretinate in psoriasis. Clinical and pharmacokinetic results of a German multicenter study. J Am Acad Dermatol. 1988 Sep;19(3):458-68.
95. van de Kerkhof PC1, Cambazard F, Hutchinson PE, Haneke E, Wong E, Souteyrand P, Damstra RJ, et alThe effect of addition of calcipotriol ointment (50 micrograms/g) to acitretin therapy in psoriasis. Br J Dermatol. 1998 Jan;138(1):84-9.
96. Olsen EAWeed WWMeyer CJCobo LM A double-blind, placebo-controlled trial of acitretin for the treatment of psoriasis. J Am Acad Dermatol 1989;21 (4, pt 1) 681- 686
97. Nikam BP, Amladi S, Wadhwa S L. Acitretin. Indian J Dermatol Venereol Leprol 2006;72:167-72
98. Shapiro J, Cohen AD, David M et al.The association between psoriasis, diabetes mellitus and atherosclerosis in Israel: a case-control study. J Am Acad Dermatol 56:629-634
99. Neimann AL, Shin DB, Wang X, Margolis DJ, Troxel AB, Gelfand JM. Prevalence of cardiovascular risk factors in patients with psoriasis. J Am Acad Dermatol 2006;55:829-35