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Comparative Study Between Methotrexate & Cyclosporine In Severe Psoriasis Vulgaris:A Study In Tertiary Care Centre Jharkhand

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Abstract: ***Background*** *: Management of severe psoriasis is difficult& no complete cure is available . Number of topical & systemic drugs are available.Methotrexate & cyclosporine have been used for the management of severe psoriasis from longer time.*
Objective *: This study was done to compare the efficacy and safety of daily cyclosporine with weekly methotrexate in the management of severe psoriasis in tertiary care centre, Jharkhand.*
Mathods*: Forty patients with severe psoriasis were randomly assigned to treatment with cyclosporine or methotrexate. The initial dose of cyclosporine was 3 mg/kg/day, which was increased to a maximum of 5 mg/kg/day after the response was not adequate, by increasing dose 1 mg/kg/day in every 2 weeks. Methotrexate was administered at a dose of 0.3 mg/kg/week. Clinical response was assessed by calculating PASI score in all patients at biweekly intervals. Patients were followed up every two weekly up to a maximum of 12 weeks. The doses of both drugs were gradually tapered once >75% reduction in disease severity was attained.*
Results*: Marked improvement (>75% reduction in PASI) was noted in all patients except for 2 in the cyclosporine group. The median time for marked improvement was 5.6 weeks with methotrexate and 7.2 weeks with cyclosporine. Patients on methotrexate were found to have more rapid and complete clearance than those on cyclosporine.*
Conclusion : *Both drugs were well tolerated. Side effects in both the treatment groups were minor, transient, and manageable. At doses with comparable safety profiles, methotrexate resulted in more rapid and cost effective clearance of patients with severe psoriasis.*
Key words: *psoriasis; methotrexate; cyclosporine.*

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I. Introduction

Psoriasis is a common, immunologically mediated, inflammatory disease characterized by skin inflammation,epidermal hyperplasia, and increased risk of painful and destructive arthritis as well as cardiovascularmorbidity and psychosocial challenges.Estimates of the occurrence of psoriasis indifferent parts of the world vary from 0.1% to 3%[1,2].Patients with mild or localized psoriasis can be managedwith topical treatment alone.Use ofsystemic therapy becomes mandatory in patientswith severe extensive disease and inthose not responding to conventional topicaltherapy[3].Various systemic therapiesthat are available include methotrexate[4],cyclosporine[5],NBUVB[6],PUVA[7],acitretin[8],fumaric acid esters[9]and hydroxyurea[10]. None of these systemicdrugs are uniformly efficacious, andthere are significant toxicities associatedwith their use.

Methotrexate(4-amino-*N* methyl pteroylglutamic acid) is a dihydrofolate reductase enzyme inhibitor. It inhibit keratinocyte proliferation by inhibiting DNA synthesis.It also hasantiinflammatory actionby inhibition of(AICAR [5-aminoimidazole-4-carboxamide ribonucleotide]transformylase), an enzyme involved in purinemetabolism. This leads to accumulation of extracellularadenosine, which has potent anti-inflammatoryactivities[11].We starts it with a test dose of 2.5 mg and then gradually increasedose until a therapeutic level is achieved (average range,10–15 mg/week or 0.1-0.3mg/kg/week, maximum, 25–30 mg weekly). It is highly effective for chronic plaque psoriasis and is also indicated for the long-termmanagement of severe forms of psoriasis, includingpsoriatic erythroderma and pustular psoriasis[4]. Methotrexate therapy for psoriasis can cause a myriad of sideeffects including nausea, bone marrow suppression, mucositis andhepatotoxicity.

Cyclosporine (CYA) is a neutral cyclic undecapeptide, derived from the fungus *Tolypocladium inflatumgams*, works by inhibiting IL-2production by lymphocytes via calcineurin inhibition. It mediates its action through immunosuppression of theintraepidermal cytotoxic T cell response by impairing the releaseof interleukin-1 and interleukin-2, which plays a major role inthe activation and proliferation of other T lymphocytes[12].The dosage ranges from 2-5mg/kg/day.Response to cyclosporine has been reported for virtually all theclinical manifestations of psoriaris[5].It is used as induction not as maintenance treatment because it has long term significant side effects.The major issues relate to renal impairment, hypertensionand possible increased risk of malignancies.

Various studies comparing the effects of cyclosporineand methotrexate in the management of severepsoriasis had been done, but gave equivocal results.

II. Methods

This was a prospective, randomized, comparative study between weekly dose of methotrexate and daily dose of cyclosporine. Duration of study was 12 months. Approval was taken by institutional ethical committee before initiating this study.40 consecutive patients indoor & outdoor patients in RIMS,Ranchi were included in this study.The patients were randomly assigned to either the MTX (Group A) or CYA (Group B) treatment groups.

- **Inclusion criteria**-
- Generalized plaque type psoriasis / severe psoriasis (>40% Body surface area involved)
- Patients with any age & sex
- Patients free from any systemic disease
- **Exclusion criteria**-
- Pregnancy, lactation
- Impaired renal or liver function, uncontrolled hypertension, epilepsy, gout
- History of malignancy
- Alcoholics
- Concomitant topical or systemic antipsoriatic therapy
- Concomitant therapy with nephrotoxic compounds such as aminoglycosides
- Concomitant therapy of drugs known to interact with CYA or MTX

- Informed written consent wasobtained from all the patients.
- A detailed history was taken and a thorough general and cutaneous examination was carried out before the start of therapy.
- The severity of disease and reponse to treatment were assessed by calculating the PASI score [13].
- **Baseline investigations**-

- CBC,LFT,RFT,Blood sugar,Routine Urine examination, serum electrolytes,serum uric acid, Serum lipid profile
- Chest X-ray,ECG
- HIV serology and HBs antigen

Patients in group A were started single weekly dose of MTX (0.3mg/kg/week).Group B patients were administered CYA in adaily divided dose of 3 mg/kg. The dose of CYAwas increased to a maximum of 5 mg/kg if therewas no change or a rise in PASI score after 2weeks of therapy.Dose increased by 1mg/kg/day in every 2 weeks.For persistently abnormal laboratory values,we followed standard guidelines for bothMTX and CYA[14,15].

Afterfour weeks of therapy, allpatients were reassessed and patients with <25%reduction of their PASI score were regarded asnon-responders.Each patient was followed up every 2 weekly, up toa period of 12 weeks. Complete physical examination,blood pressure recording, PASI scoring,urine examination, serum electrolytes, liver andrenal function tests were carried out at eachvisit. Serum uric acid and lipid profile were carriedout at four weekly intervals.

The dose ofCYA or MTX was tapered once >75% reductionin PASI score was attained.
Response to therapy graded as-

Grades	(% Reduction in PASI Score)
Mild	<50 %
Moderate	50-75 %

Severe >75 %

Statistical analysis
Results between the two groups were analysed by unpaired Students t-test and chi-square test. Within group comparison was carried out usingpaired Students t-test.

III. Results

The mean age of patients in Group A was38.7 ± 4 years (18–60 years). In Group B, theage ranged between 19–60 years and themean age was 42.2 ± 3 years. More detailedphysical characteristics of patients from thetwo study groups are listed Table 1.The weekly dose of MTX ranged from15–30 mg (mean 26.8 ± 0.9 mg). The dailydose of CYA ranged from 125–300 mg(mean 191.6 ± 8.6 mg).

Clinical Response
All the patients showed moderate tomarked improvement.Clinical response is seen in Figure 1 to 4. The extent of skin involvementsteadily decreased from the baselinein both groups resulting in 95.6% reductionin mean PASI in Group Aand82.6% reduction of PASI in Group B after12 weeks of therapy (Chart 1).

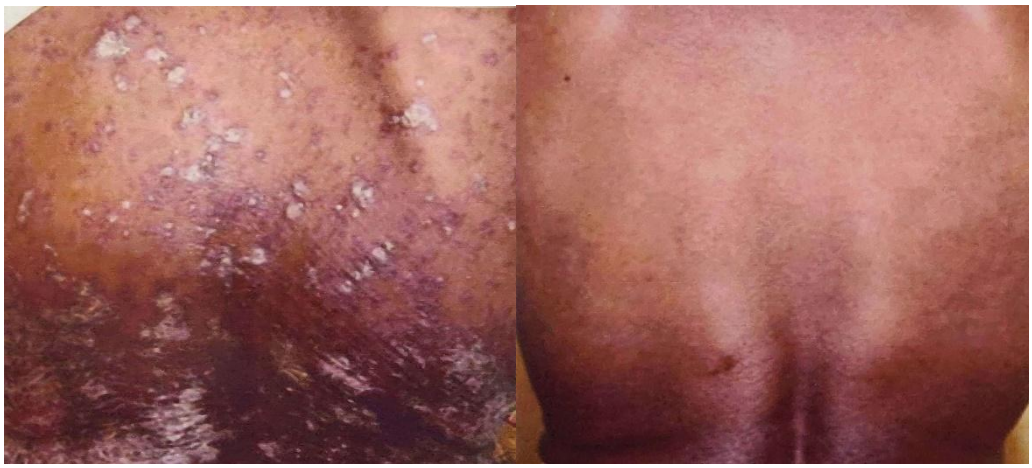

Figure-1
Before treatment

Figure-2
After treatment

Group-A – 12 weeks of Methotrexate therapy

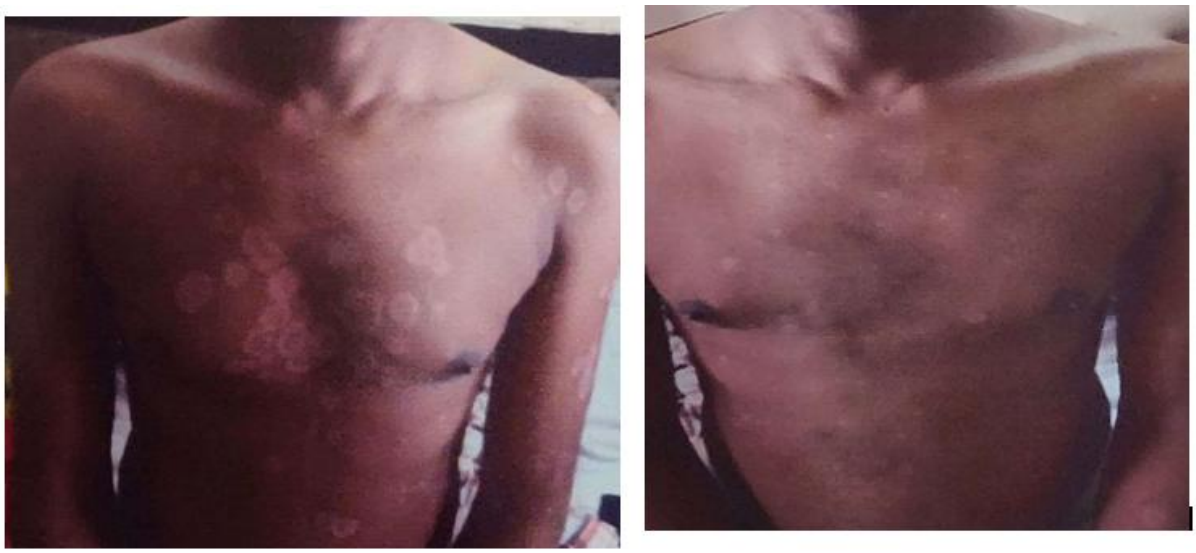

Figure-3
Before treatment

Figure-4
After treatment

Group B-12 weeks of Cyclosporine therapy

Reductions in mean PASI in both groupsare given in Table 2. The differences in theresponse between the two treatment groupsacquired statistical significance at 2,4, 6, and12 weeks ($p<0.05$). To achieve satisfactoryresults, the initial dose of CYA had to be increasedin 9/20 (45%) patients. Therewere no differences in age of onset, durationof disease or previous systemic therapiesin patients requiring the higher dose.In these nine patients in whom the dosewas increased after about four weeks the responsebecame comparable to the rest of the patients who did not require increaseddoses. The subsequent fall in PASI was alsocomparable to that of the rest of the patientsin the CYA treated group.

Table 1. Pretreatment characteristics ofpatients in both groups

	MTX	CYA
Age (years)*	38.7+/-4	42.2+/-3
Sex ratio	5:1	6.7:1
Duration (months)*	66.5+/-13.5	63.4+/-3.2
Age at onset of disease (years)*	34.7+/-4.2	42.3+/-3.1
Body surface area (%)*	71.4%	72.7%
Baseline PASI*	26.3+/-2.1	27.6+/-1.9
Nail involvement (%)	11/20 (55%)	9/20 (45%)
Joint involvement (%)	2/20 (10%)	3/20 (15%)
Type of psoriasis plaque (%)	14/20 (70%)	14/20 (70%)
Erythroderma (%)	5/20 (25%)	5/20 (25%)

*Mean+/-S.E.M.

Table 2. Reduction in PASI (Mean ± S.E.M) in both groups (% PASI reduction in each group)

Duration (in weeks)	Group A	Group B
0	0	0
2	38	20
4	64.5	45.4
6	84.7	70.2
8	89.3	88.6
10	93.3	89.3
12	95.6	82.6

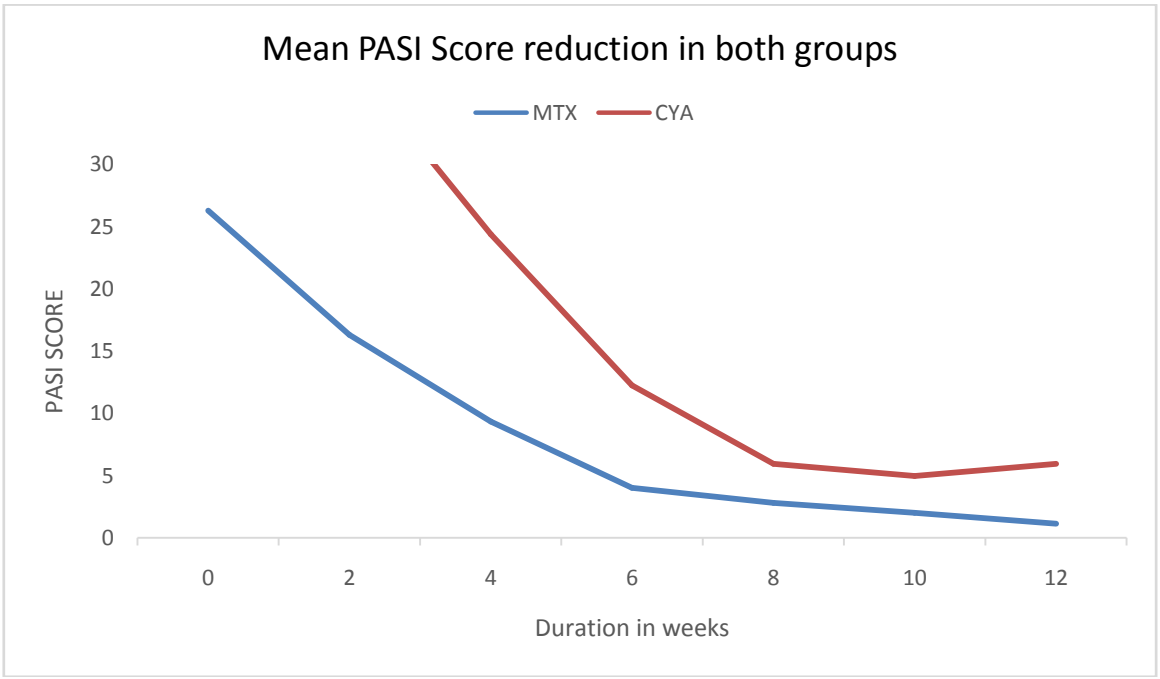

Chart 1.

The mean time at which >75% reductionin PASI score occurred was 5.6 weeks (range2–12 weeks) in the methotrexate group and7.2 weeks (range 4–10 weeks) in the CYAgroup ($p<0.05$). In the MTX group, 17/20(85%) patients achieved complete clearanceand remained clear of their lesions asthe dose was tapered. In

the CYA group,only 8/20 (40%) patients attained completeclearance. A gradual rise in PASI score wasseen in 15/20 of patients as the dose was tapered,and only 5 patients remained clearof their lesions at twelve weeks.

In the cyclosporine group, the readingsfor systolic pressure remained stablethroughout the study. Four of our 20 patientsdeveloped diastolic hypertension,2patients during the first week of therapy andone each in the third and sixth week. Thesepatients were well controlled with anti-hypertensivedrugs.There were slight increases (4–14%) inserum creatinine levels, they however didnot go beyond the stipulated >30% rise inserum creatinine requiring a reduction inthe dose of cyclosporine. Once the dose ofcyclosporine was tapered, the serum creatininelevels showed a downward trend.

Other biochemical parameters includinghemogram, LFT, RFT, serum electrolytes,serum cholesterol, and serum uric acid didnot alter in any patient on either therapy.

In the MTX group, 4/20 (20%) patientsreported mild nausea and vomiting ontheday of methotrexate administration; it couldbe managed satisfactorilywith antiemetics.Fatigue, headache and giddiness were notedin one patient each. In the cyclosporinegroup, in addition to hypertension, four(20%) patients suffered from mild headacheand decreased sleep in the initial periodof therapy; this subsided as the treatmentcontinued.

IV. Discussion

We conducted this study according to international guidelines that have developed for both treatments[14,15]. Methotrexate & cyclosporine both have well documented efficacy for management of severe psoriasis. Both can be used in a largemajority of patients,but have some contraindications[16,17]. In any of two drug is contraindicated, other drug can be used,because both drugs causes rapid reduction in the severity ofdisease[18–20, 22–25].

In our study, all 20 patients in theMTX group showed >75% reduction inPASI within a mean duration of 5.6 weeks.The response in our patients was similar tothose reported by Kamaljeet et al[21]andRoenigk et al.[24], who observed markedimprovement in 80–91% of their patientswithin 3–6 weeks of therapy. In our study,complete clearance was noted in 17/20(85 %) patients on MTX. Conversely, instudies by Rees et al.[23] and Roenigk et al[24], the response was slower, and completeclearance was noted in only 45–60% of thepatients on weekly methotrexate therapy.All the 17 patients who attained completeclearance remained free of their lesionseven after gradual reduction in thedose of methotrexate. This is in conformitywith other studies in which prolonged clearancewith methotrexate therapy has beenreported[22–25].

In the CYA group, all the patients except2 showed marked improvement. Only amoderate response (50–75% reduction inPASI) was noted in 2 patient. The dosehad to be increased in 9/20 (46.6%) patientsafter two weeks because of an unsatisfactoryresponse at a dose of 3 mg/kg/day. Thisobservation is similar to the study by Kamaljeet et al[21] and Mahrleet al[26]. In later study , 34% of the patientstreated with an initial dose of 2.5 mg/kg/day requiredan increase in dosage in order toachieve a good response. All our patients excepttwo showed a marked response oncetheir dose was increased. Patients requiring dose escalationhad same charactersitics from the rest,Soit can be concluded thatthe response is mostly dose dependentfor both good andmoderate responders to cyclosporine therapy.Complete clearance was noted inonly 8/20 (40%) patients. Marked improvement were noted with mean duration of 7.2 inour study is comparable withprevious studies reporting similar responsesin 6–8 weeks. As the dose of CYAwas tapered, there was a 6.7% rise in PASI scoreby the end of the study (12 weeks) as comparedwith the scores at ten weeks in two patients.

In CYA group, Mean reduction in PASIwas only marginal at four weeks as compare to MTX groupdue to lack of response tothe initial dose in 9 patients of CYA group. In theMTX group, 50% of patients achieved amarked response by four weeks as comparedto 13% in the CYA group. In MTX group almost 85 % reduction were noted in mean PASI Score at 6 weeks, As compared to 70 % in CYA group. After eight weeks oftherapy, the responses with both MTX andCYA were comparable. The fall in PASI inthe MTX group was rapid and consistentthroughout the study period unlike that observedin the CYA group. Complete clearancewas also noted more often in the MTXgroup (85%); in the CYA group, only halfof this number (40%) had complete clearanceof lesions. Even on tapering the dose,all the patients on MTX remained free ofdisease at twelveweeks. In contrast, a rise inPASI was observed in 15/20 CYA-treated patientsonce the drug was tapered.

Overall tolerability to both of drugs was good.Most common adverse effects were gastrointestinal inthe MTX group similar to previous studies[22–25]. The major limiting side effectof cyclosporine treatment is nephrotoxicity,which is usually reversible. In our study,none of the patients had rises in serum creatininevalues, which exceeded the uppermostlimit of the normal range. Increases of4–14% in the level were noted. Similarfindings were reported by Finzi et al[27].Hypertension is another common side effectof cyclosporine therapy[5]. In thecyclosporine group, clinically significantmild diastolic hypertension was observed in4/20 (20%) patients who required antihypertensivetherapy. Our results are similar tothose of Van Joost et al.[28] who reportedmild hypertension in 5 of their 18 patients.This hypertensive effect did not seem to bedirectly related to dose; two patients developedhypertension even though their dosewas not increased. This confirms anotherstudy

in which the incidence of hypertensionwas not found to be dose dependent[29]. However Powles et al.[30] did find hypertensionto be dose dependent in theirstudy.

V. Conclusion

In this study, Both drugs showed comparable profile. All of the side effects observedwere minor, transient, and easily managed.Although cyclosporine has been advocatedas a crisis intervention drug in severepsoriasis. In our study, methotrexate was found to inducea more rapid and complete remission. Thus, in doses with comparablesafety profiles methotrexate is the preferreddrug for rapid and cost effective clearanceof patients with severe psoriasis. Cyclosporinecan provide an effective alternative inpatients who do not tolerate or in whommethotrexate therapy is contraindicated.

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