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.

Methods: 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 complete 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 cardiovascular morbidity and psychosocial challenges. Estimates of the occurrence of psoriasis in different parts of the world vary from 0.1% to 3%². Patients with mild or localized psoriasis can be managed with topical treatment alone. Use of systemic therapy becomes mandatory in patients with severe extensive disease and those not responding to conventional topical therapy. Various systemic therapies that are available include methotrexate⁴, cyclosporine⁵, NBUVB⁶, PUVA⁷, acitretin⁸, fumaric acid esters⁹, and hydroxyurea¹⁰. None of these systemic drugs are uniformly efficacious, and there are significant toxicities associated with their use.

Methotrexate (4-amino-N-methyl pteroylglutamic acid) is a dihydrofolate reductase enzyme inhibitor. It inhibits keratinocyte proliferation by inhibiting DNA synthesis. It also has anti-inflammatory action by inhibition of (5-aminoimidazole-4-carboxamide ribonucleotide transformylase), an enzyme involved in purinemetabolism. This leads to accumulation of extracellular adenosine, which has potent antiinflammatory activities. We start it with a test dose of 2.5 mg and then gradually increase dose until a therapeutic level is achieved (average range, 10–15 mg/week or 0.1–0.3 mg/kg/week, maximum, 25–30 mg weekly). It is highly effective for chronic plaque psoriasis and is also indicated for the long-term management of severe forms of psoriasis, including psoriatic erythroderma and pustular psoriasis. Methotrexate therapy for psoriasis can cause a myriad of side effects including nausea, bone marrow suppression, mucositis and hepatotoxicity.
Cyclosporine (CYA) is a neutral cyclic undecapeptide, derived from the fungus *Tolypocladium inflatum gams*, works by inhibiting IL-2 production by lymphocytes via calcineurin inhibition. It mediates its action through immunosuppression of the intraepidermal cytotoxic T cell response by impairing the release of interleukin-1 and interleukin-2, which plays a major role in the activation and proliferation of other T lymphocytes \(^4\). The dosage ranges from 2-5mg/kg/day. Response to cyclosporine has been reported for virtually all the clinical manifestations of psoriasis \(^5\). It is used as induction not as maintenance treatment because it has long-term significant side effects. The major issues relate to renal impairment, hypertension, and possible increased risk of malignancies.

Various studies comparing the effects of cyclosporine and methotrexate in the management of severe psoriasis 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 was obtained 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 response 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 a daily divided dose of 3 mg/kg. The dose of CYA was increased to a maximum of 5 mg/kg if there was no change or a rise in PASI score after 2 weeks of therapy. Dose increased by 1mg/kg/day in every 2 weeks. For persistently abnormal laboratory values, we followed standard guidelines for both MTX and CYA \(^14,15\).

After four weeks of therapy, all patients were reassessed and patients with <25% reduction of their PASI score were regarded as non-responders. Each patient was followed up every 2 weekly, up to a period of 12 weeks. Complete physical examination, blood pressure recording, PASI scoring, urine examination, serum electrolytes, liver and adrenal function tests were carried out at each visit. Serum uric acid and lipid profile were carried out at four weekly intervals.

The dose of CYA or MTX was tapered once >75% reduction in PASI score was attained.

Response to therapy graded as-

<table>
<thead>
<tr>
<th>Grades</th>
<th>(% Reduction in PASI Score)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>&lt;50%</td>
</tr>
<tr>
<td>Moderate</td>
<td>50-75%</td>
</tr>
</tbody>
</table>
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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 using paired Students t-test.

III. Results

The mean age of patients in Group A was 38.7 ± 4 years (18–60 years). In Group B, the age ranged between 19–60 years and the mean age was 42.2 ± 3 years. More detailed physical characteristics of patients from the two study groups are listed Table 1. The weekly dose of MTX ranged from 15–30 mg (mean 26.8 ± 0.9 mg). The daily dose of CYA ranged from 125–300 mg (mean 191.6 ± 8.6 mg).

Clinical Response
All the patients showed moderate to marked improvement. Clinical response is seen in Figure 1 to 4. The extent of skin involvement steadily decreased from the baseline in both groups resulting in 95.6% reduction in mean PASI in Group A and 82.6% reduction of PASI in Group B after 12 weeks of therapy (Chart 1).

Figure 1
Before treatment

Figure 2
After treatment

Figure 3
Before treatment

Figure 4
After treatment

Group-A – 12 weeks of Methotrexate therapy
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Group B-12 weeks of Cyclosporine therapy

Reductions in mean PASI in both groups are given in Table 2. The differences in the response between the two treatment groups acquired statistical significance at 2, 4, 6, and 12 weeks (p<0.05). To achieve satisfactory results, the initial dose of CYA had to be increased in 9/20 (45%) patients. There were no differences in age of onset, duration of disease or previous systemic therapies in patients requiring the higher dose. In these nine patients in whom the dose was increased after about four weeks the response became comparable to the rest of the patients who did not require increased doses. The subsequent fall in PASI was also comparable to that of the rest of the patients in the CYA treated group.

Table 1. Pretreatment characteristics of patients in both groups

<table>
<thead>
<tr>
<th></th>
<th>MTX</th>
<th>CYA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>38.7±/4</td>
<td>42.2±/3</td>
</tr>
<tr>
<td>Sex ratio</td>
<td>5:1</td>
<td>6:7:1</td>
</tr>
<tr>
<td>Duration (months)</td>
<td>66.5±/13.5</td>
<td>63.4±/3.2</td>
</tr>
<tr>
<td>Age at onset of disease (years)</td>
<td>34.7±/4.2</td>
<td>42.3±/3.1</td>
</tr>
<tr>
<td>Body surface area (%)</td>
<td>71.4%</td>
<td>72.7%</td>
</tr>
<tr>
<td>Baseline PASI</td>
<td>26.3±/2.1</td>
<td>37.6±/1.9</td>
</tr>
<tr>
<td>Nail involvement (%)</td>
<td>11/20 (55%)</td>
<td>9/20 (45%)</td>
</tr>
<tr>
<td>Joint involvement (%)</td>
<td>2/20 (10%)</td>
<td>3/20 (15%)</td>
</tr>
<tr>
<td>Type of psoriasis plaque (%)</td>
<td>14/20 (70%)</td>
<td>14/20 (70%)</td>
</tr>
<tr>
<td>Erythroderma (%)</td>
<td>5/20 (25%)</td>
<td>5/20 (25%)</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Duration (in weeks)</th>
<th>Group A</th>
<th>Group B</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>38</td>
<td>20</td>
</tr>
<tr>
<td>4</td>
<td>64.5</td>
<td>45.4</td>
</tr>
<tr>
<td>6</td>
<td>84.7</td>
<td>70.2</td>
</tr>
<tr>
<td>8</td>
<td>89.3</td>
<td>88.6</td>
</tr>
<tr>
<td>10</td>
<td>93.3</td>
<td>89.3</td>
</tr>
<tr>
<td>12</td>
<td>95.6</td>
<td>82.6</td>
</tr>
</tbody>
</table>

Chart 1.

The mean time at which >75% reduction in PASI score occurred was 5.6 weeks (range 2–12 weeks) in the methotrexate group and 7.2 weeks (range 4–10 weeks) in the CYA group (p<0.05). In the MTX group, 17/20 (85%) patients achieved complete clearance and remained clear of their lesions as the dose was tapered. In
the CYA group, only 8/20 (40%) patients attained complete clearance. A gradual rise in PASI score was seen in 15/20 of patients as the dose was tapered, and only 5 patients remained clear of their lesions at twelve weeks.

In the cyclosporine group, the readings for systolic pressure remained stable throughout the study. Four of our 20 patients developed diastolic hypertension, 2 patients during the first week of therapy and one each in the third and sixth week. These patients were well controlled with anti-hypertensive drugs. There were slight increases (4–14%) in serum creatinine levels, they however did not go beyond the stipulated >30% rise in serum creatinine requiring a reduction in the dose of cyclosporine. Once the dose of cyclosporine was tapered, the serum creatinine levels showed a downward trend.

Other biochemical parameters including hemogram, LFT, RFT, serum electrolytes, serum cholesterol, and serum uric acid did not alter in any patient on either therapy.

In the MTX group, 4/20 (20%) patients reported mild nausea and vomiting on the day of methotrexate administration; it could be managed satisfactorily with antiemetics. Fatigue, headache and giddiness were noted in one patient each. In the cyclosporine group, in addition to hypertension, four (20%) patients suffered from mild headache and decreased sleep in the initial period of therapy; this subsided as the treatment continued.

IV. Discussion

We conducted this study according to international guidelines that have developed for both treatments. Methotrexate & cyclosporine both have well documented efficacy for management of severe psoriasis. Both can be used in a large majority of patients, but have some contraindications. In any of two drugs is contraindicated, other drug can be used, because both drugs causes rapid reduction in the severity of disease.

In our study, all 20 patients in the MTX group showed >75% reduction in PASI within a mean duration of 5.6 weeks. The response in our patients was similar to those reported by Kamaljeet et al. (22) and Roenigk et al. (24), who observed marked improvement in 80–91% of their patients within 3–6 weeks of therapy. In our study, complete clearance was noted in 17/20 (85%) patients on MTX. Conversely, in studies by Rees et al. (23) and Roenigk et al. (24), the response was slower, and complete clearance was noted in only 45–60% of the patients on weekly methotrexate therapy. All the 17 patients who attained complete clearance remained free of their lesions seven after gradual reduction in the dose of methotrexate. This is in conformity with other studies in which prolonged clearance with methotrexate therapy has been reported.

In the CYA group, all the patients except 2 showed marked improvement. Only an amoderate response (50–75% reduction in PASI) was noted in 2 patients. The dose had to be increased in 9/20 (46.6%) patients after two weeks because of an unsatisfactory response at a dose of 3 mg/kg/day. This observation is similar to the study by Kamaljeet et al. (21) and Mahrleet al. (26). In later study, 34% of the patients treated with an initial dose of 2.5 mg/kg/day required an increase in dosage in order to achieve a good response. All our patients except two showed a marked response. Once their dose was increased. Patients requiring dose escalation had same characteristics from the rest. So it can be concluded that the response is mostly dose dependent for both good and moderate responders to cyclosporine therapy. Complete clearance was noted in only 8/20 (40%) patients. Marked improvement were noted with mean duration of 7.2 in our study is comparable with previous studies reporting similar responses in 6–8 weeks. As the dose of CYA was tapered, there was a 6.7% rise in PASI score by the end of the study (12 weeks) as compared with the scores at ten weeks in two patients.

In CYA group, Mean reduction in PASI was only marginal at four weeks as compared to MTX group due to lack of response to the initial dose in 9 patients of CYA group. In the MTX group, 50% of patients achieved marked response by four weeks as compared to 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 of therapy, the responses with both MTX and CYA were comparable. The fall in PASI in the MTX group was rapid and consistent throughout the study period unlike that observed in the CYA group. Complete clearance was also noted more often in the MTX group (85%); in the CYA group, only half of this number (40%) had complete clearance of lesions. Even on tapering the dose, all the patients on MTX remained free of disease at twelve weeks. In contrast, a rise in PASI was observed in 15/20 CYA-treated patients once the drug was tapered.

Overall tolerability to both of drugs was good. Most common adverse effects were gastrointestinal in the MTX group similar to previous studies. The major limiting side effect of cyclosporine treatment is nephrotoxicity, which is usually reversible. In our study, none of the patients had rises in serum creatinine values, which exceeded the uppermost limit of the normal range. Increases of 4–14% in the level were noted. Similar findings were reported by Finzi et al. (27). Hypertension is another common side effect of cyclosporine therapy. In the cyclosporine group, clinically significant mild diastolic hypertension was observed in 4/20 (20%) patients who required antihypertensive therapy. Our results are similar to those of Van Joost et al. (28) who reported mild hypertension in 5 of their 18 patients. This hypertensive effect did not seem to be directly related to dose; two patients developed hypertension even though their dose was not increased. This confirms another study
in which the incidence of hypertension was not found to be dose dependent\cite{29}. However Powles et al.\cite{30} did find hypertension to be dose dependent in their study.

V. Conclusion

In this study, both drugs showed comparable profile. All of the side effects observed were minor, transient, and easily managed. Although cyclosporine has been advocated as a crisis intervention drug in severe psoriasis, in our study, methotrexate was found to induce more rapid and complete remission. Thus, in doses with comparable safety profile methotrexate is the preferred drug for rapid and cost-effective clearance of patients with severe psoriasis. Cyclosporine can provide an effective alternative in patients who do not tolerate or in whom methotrexate therapy is contraindicated.

References


