EFFECTIVENESS AND SAFETY PROFILE OF CYCLOSPORIN A IN RHEUMATOID ARTHRITIS

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ABSTRACT

Objectives: *To describe the effectiveness and safety profile of Cyclosporine A in the treatment of Rheumatoid Arthritis.*

Methodology: *The study was conducted in the department of Medicine, Khyber Teaching Hospital from Sep 98 to Aug 99. There was three months recruitment period i.e. July to September prior to the actual treatment phase. Those patients that fulfilled the criteria of the American College of Rheumatology for Rheumatoid Arthritis were included in the study. A total of 25 patients with Rheumatoid Arthritis (RA) completed the study. Patients started on Cyclosporine A were followed for a period of one year.*

Results: *Outcome was assessed in respect of functional grade and joint score during the study and at the end of one year and was graded as very good, good and poor. Sixty percent patients showed very good to good response to Cyclosporine treatment, as they were in functional class 1 and showed more than 80% reduction in joint score. The other 40% had poor response as they were in functional class 2 or more and had less than 80% reduction in joint score.*

Mild hypertension was seen in 2 (8%) patients. Two (8%) patients developed hypertrichosis. One patient with severe gingival hyperplasia eventually dropped out of the study. None of the patients showed elevation of serum creatinine level above 30% of the baseline values at any time during treatment.

Conclusion: *The study shows that Cyclosporine A is an effective agent in active and potentially disabling RA. It has a good safety profile when used in recommended doses.*

Key words: *Rheumatoid Arthritis, Cyclosporine A, Functional Grade, Joint score.*

INTRODUCTION

Rheumatoid Arthritis (RA) is a chronic multisystem disorder of unknown etiology that can lead to destructive joint disease. Although there are a variety of systemic manifestations, the characteristics feature of Rheumatoid Arthritis is persistent inflammatory synovitis usually involving peripheral joints in symmetric distribution. The potential of the synovial inflammation to cause cartilage destruction, bone erosion and subsequent changes in joint integrity is the hallmark of the disease. Despite its destructive potential, the course of the disease can be quite variable, ranging from a mild oligoarthritis to a relentlessly progressive polyarthritis[1, 2].

The American Rheumatism Association 1987 devised revised criteria for the classification of rheumatoid arthritis. It is having 7 parameters as follows: 1) morning stiffness in and around joints lasting at least 1 hour before maximal improvement; 2) soft tissue swelling (arthritis) of 3 or more joint areas observed by a physician; 3) swelling (arthritis) of the proximal interphalangeal, metacarpophalangeal, or wrist joints; 4) symmetric swelling (arthritis); 5) rheumatoid nodules; 6) the presence of rheumatoid factor; and 7) radiographic erosions and/or periarticular osteopenia in hand and/or wrist joints. Criteria 1 through 4 must have been present for at least 6 weeks. Rheumatoid arthritis is defined by the presence of 4 or more criteria, and no further qualifications (classic, definite, or probable) or list of exclusions are required[3].

The etiology of RA is not known but it is certain that the process is mediated by immunological mechanisms and both cellular as well as humoral immunity play a role in the

causation of the disease. Immunosuppressive and Disease Modifying Antirheumatic Drugs (DMARDs) are therefore of benefit in the treatment of RA[1,4]. These drugs include methotrexate, hydroxychloroquine, penicillamine, gold, cyclosporine A, sulphasalazine, azathioprin and more recently the biological DMARDs (etanercept, infliximab, and adalimumab)[5]. DMARDs improve both the clinical and laboratory indices of the disease. There is evidence that radiographic progression of RA is slowed with DMARDs[6,7]. The immunopathogenesis of RA is the early activation of the T-cells and the subsequent involvement of other populations as the disease progresses. Cyclosporine A blocks the transcription of key T-cell cytokines such as IL-2 and thus inhibits T-cell activation[8].

Recent data suggest that Interleukin (IL)-15 also plays an important role in the pathogenesis of rheumatoid arthritis. IL-15 may exert its pro inflammatory properties via the induction of IL-17, a cytokine known to stimulate synoviocytes to release several mediators of inflammation including IL-6, IL-8, GM-CSF and PGE_2. IL-17 secretion is completely or partially blocked in the presence of low doses of cyclosporin A[9]. Cyclosporin except for its renal toxicity is effective in the treatment of RA[10]. It has been suggested that efficacy and tolerability of slow acting agents such as Cyclosporine A is increased when they are used early in the disease course. The results of studies indicate that early Cyclosporine A therapy is associated with longer survival on treatment, fewer side effects, slower disease progression (demonstrated radiologically) and most importantly fewer first erosions.[11, 12]. Cyclosporin A can be used alone or in combination with other DMARDs particularly in the early stages of moderate to severe RA[13]. There are quite a few side effects of Cyclosporin A, but they are dose dependant and may be alleviated by the dosage reduction[14]. The most frequent side effects are abdominal pain with cramps, diarrhea, edema, gingival hyperplasia, tremors, hirsutism, hypertension, and nephrotoxicity[15].

The purpose of our study was to describe the effectiveness and safety profile of Cyclosporine A in the treatment of Rheumatoid Arthritis.

METHODOLOGY

The study was conducted in the department of Medicine, Khyber Teaching Hospital, Peshawar from September 1998 to August 1999. There was three months recruitment phase prior to the actual treatment phase. Patients were enrolled consecutively. The last patient was recruited at the end of August 1998. Informed consent was obtained from all patients and they also received instructions regarding the nature of the treatment.

Patients that fulfilled the 1987 American College of Rheumatology revised criteria for Rheumatoid Arthritis and between the ages of 16 and 65 years were included in the study. Patients with progressive active Rheumatoid Arthritis not responding to adequate doses of non steroidal anti-inflammatory drugs (NSAIDs) and disease modifying anti-Rheumatic drugs (DMARDs) and those having severe disabling disease with radiological evidence of erosions were enrolled in the study. Patients having intolerable side effects of NSAIDs or other DMARDs therapy were also included.

The Exclusion criteria comprised of pregnant or lactating mothers, patients with renal dysfunction (elevated serum creatinine i.e.>1.2mg/dl), history of hypertension (systolic BP> 160 mm Hg, diastolic > 90 mm Hg), presence or history of previous malignancy, major complicating illness like amyloidosis, heart or lung diseases, Immunodeficiencies and blood cytopenias and patients with elevated transaminases and or Bilirubin (more than twice the upper limit of normal).

Detailed history was taken of the activity and duration of the disease and of the medications used. Meticulous clinical examination was performed, looking for both articular, extra articular manifestations and complication of the disease. Erythrocyte sedimentation rate (ESR), C reactive protein (CRP), RA Factor and x-ray of the involved joints were done. Other investigations included full blood count (FBC), platelets count, urea, creatinine, liver function tests (LFTS), uric acid, urinalysis and pregnancy test in females of childbearing age. Most of the patients were admitted to hospital for their first dose. The initial dose of cyclosporine A was 2.5 mg/kg/day given in two divided doses. The dose was then titrated according to the response of the patients. After starting treatment with Cyclosporine A, patients were first followed up regularly each week for their first four weeks and then at monthly interval for up to three months and then every three months up till one year. On each follow up visits clinical assessment was done to assess the following.

i. Duration of morning stiffness

ii. Grip strength

iii. Number of joints with both tenderness and swelling

iv. Number of swollen joints

v. Number of tender joints

vi. Assessment of pain on visual analogue scale.

vii. Physician's overall assessment of disease activity

viii. Patients overall assessment of disease activity

ix. Degree of disability

Blood pressure and the concurrent use of other medications were recorded at baseline and at follow up visits. Side effects of medications including hypertension, extra hair growth and gingival hyperplasia others were looked for. In addition investigations including ESR and CRP were done to monitor disease activity and drug side effects.

The functional grade (class) of the patient was assessed as per the revised criteria devised by the American college of Rheumatology as follows[16]. Class I = able to perform usual activities of daily living. Class II = able to perform usual self-care and vocational activities, but limited in avocational activities. Class III = able to perform usual self-care activities but limited in vocational and avocational activities; class IV = limited in ability to perform usual self-care, vocational, and avocational activities.

The overall response at the end of the study was graded from very good to good and poor. Very good response:- Patients with functional grade-1 without concomitant analgesics and steroids and who showed ≥80% reduction in joint score. i.e. the sum of number of painful, tender and swollen joints. Good response:- Functional grade 1-2 with concomitant analgesics and or steroids who showed ≥ 80% reduction in joint score. Poor response:- Functional grade >2 with concomitant analgesics and steroids who showed < 80% reduction in joint score.

RESULTS

A total of thirty patients were initially enrolled in the study. One patient dropped out because of drug related side effects. Four patients did not keep up the follow up appointment and were taken out of the final outcome analysis. Twenty five patients completed this study, 8 males and 17 females. The average age was 38.5 years; average weight of the patients was 62 kgs, while the average duration of the disease was 3.27 years. Six (24%) patients were already on DMARDS. The commonly reported previous DMARDS were Sulphasalazine and Methotrexate. Most patients were using steroids in variable doses before the study. Only 3 (12%) patients could be completely weaned off steroids while in remaining 22 (88%) patients steroid dose was reduced. Twelve (48%) were kept on lowest possible dose of 5mg/day while 10 (40%) were kept on 10 to 15mg/d.

Table 1: Showing the pre-treatment and on-treatment disease activity

Clinical Criteria Morning Stiffness*	Week 0 +++++	Week 4 +++	Week 8 ++	Week 12 +	Week 24 -	Week 36 -	Week 52 -
Number of painful joints*	N=156	N=105 (n-51) 32.6%	N=89 (n-67) 42.9%	N=73 (n-59) 53.2%	N=56 (n-100) 64.1%	N=49 (n-107) 68.5%	N=44 (n-112) 71.7%
Number of swollen joints*	N=132	N=84 (n-48) 36.3%	N=73 (n-59) 44.6%	N=60 (n-72) 54.5%	N=36 (n-96) 72.7%	N=32 (n-100) 75.7%	N=34 (n-98) 74.2%
Number of tender joints*	N=156	N=103 (n-53) 33.9%	N=90 (n-66) 42.3%	N=46 (n-110) 70.5%	N=42 (n-114) 73%	N=39 (n-117) 75%	N=39 (n-117) 75%
Hand Grip Strength	<50 100%	<50 92%	<50 73%	>50&<150 44%	>50&<200 39%	>50&<200 76%	>50&<200 76%

*Shows mean value, N shows total number of involved joints and the (n) show improvement in the number of joints with treatment at different intervals. Hand Grip (mm Hg) was checked on the side which was involved more initially.

Table 2: Showing radiological changes. Pre- and on treatment with Cyclosporin

	Week 0	Week 4	Week 8	Week 12	Week 24	Week 36	Week 52
Patients with joint erosions	8 (32%)	8 (32%)	8 (32%)	8 (32%)	8 (32%)	8 (32%)	8 (32%)
Patientswith damaged joints (without joint erosions)*	17 (68%)	17 (68%)	15 (60%)	15 (60%)	12 (48%)	10 (40%)	10 (40%)
Mean Damaged joint score	69	69	61	60	42	42	42
Mean eroded joint count	22	22	22	21	21	21	20
Mutilated joints	0	0	0	0	0	0	0

* Soft tissue swelling, joint space narrowing, juxta-articular osteoporosis

Table 3: Showing effect on acute phase reactants

	Week 0	Week 4	Week 8	Week 12	Week 24	Week 36	Week 52
ESR*	116	116	102	86	79	79	79
CRP*	+ve	+ve	+ve	+ve	-ve	-ve	-ve

* denotes mean value

Three (12%) patients were completely well on the Cyclosporine dose of 2.5 mg/kg/day for up to six months and in these patients it was possible to reduce the dose to 2 mg/kg/day for the next six months with the same result. Only in 6 (24%) patients, the dose was increased to a maximum of 5 mg/kg/day. In 4(16%) patients the dosage was reduced (3 patients) or discontinued (1 patient) due to undesirable effects of the drug. After 3 months of cyclosporine therapy, 18 (72%) patients were using analgesics and NSAIDs on as and when required basis and in doses lower than at the start of the study.

Response of the patients: Patients started to show improvement in 2-12 weeks time, the overall response ranging from very good to good and poor as elaborated above. Three (12%) patients showed very good response. Twelve (48%) patients showed good response. Ten (40%) showed poor response at the end of the study. At the end of one year, improvement in painful joint count was 71.7% and in the number of swollen and tender joint was 74% and 75% respectively (Table 1).

There was also slowing of the radiological disease progression in RA (Table 2).

There was significant reduction in biomarker of acute inflammation. There was 37 mm in 1st hour reduction in ESR and the CRP became negative. The RA factor remained positive throughout the study period (Table 3).

Adverse effects of the drug: Four (16%) patients had nausea and vomiting during early stages of the treatment and were managed symptomatically. Mild hypertension was seen in 2 (8%) patients. Their mean systolic pressure was 145$\pm$ 5.1 mm Hg (140-150 mm Hg) and Diastolic Pressure was 94$\pm$ 4.1 mm Hg (90-100 mm Hg). The mean BP of Cyclosporine A treated patients before treatment was 122 $\pm$ 7.2 mm Hg (Systolic) and 81$\pm$ 5.1 mm Hg (Diastolic). After 12 months of therapy, the mean BP in patients who did not develop hypertension was 125 $\pm$ 6.1 mm Hg (systolic) and 82 $\pm$ 4.9 mm Hg (diastolic). Two (8%) patients developed hypertrichosis. One patient with severe gingival hyperplasia has to discontinue the drug and dropped out of the study. None of the patients showed serum creatinine level above 30% of the baseline values at any time and none developed hyperuricemia or hyperkalemia.

DISCUSSION

Cyclosporine A was first used in 1979 by Hermann and Muller who treated a cohort of seven patients and found appreciable improvement in five patients[17]. The results of our study also show that patients with Rheumatoid Arthritis who had only partial response to nonsteroidal anti-inflammatory drugs and other disease modifying anti rheumatic drugs, observed clinically significant improvement when Cyclosporine A was used for their treatment. The effect of Cyclosporine A in our trial was comparable to that

reported for other agents such as gold, methotrexate and D-penicillamine[18]. This study also showed that Cyclosporin A could slow radiological disease progression in RA, thus confirming its disease modifying properties. These latter findings are in agreement with those reported by Foirre et al[19] and more recently by Pasero et al[20]. Studies conducted in our setup using Cyclosporine either alone or in combination with Methotrexate in the treatment of Rheumatoid Arthritis have supported our results of its efficacy[21, 22].

Correlation was also found between clinical improvement and a decrease in the acute phase response i.e. CRP and ESR. There was 32% reduction in average ESR and the CRP became negative in most of the patients. Similar results have been reported by Drosos et al[11]. Another study by Dougados et al[10] has found no correlation between clinical improvement and the ESR. It's possible that a change in the acute phase reaction is more easily detected in early Rheumatoid Arthritis. Moreover the suppressive effect of low dose prednisolone on the inflammatory response in the early stages of the disease is another possible explanation for the decrease in ESR and CRP in our study. Rheumatoid factor remained positive throughout in our patients as was the case in the study of Dougados et al[10].

Tolerability and safety of Cyclosporin A appeared to be much better in our study than that reported by others [23, 24]. Only two (8%) of our patients developed mild hypertension while in Tugwell[24] study 22% patients developed hypertension. In yet another study of Italian group[25], hypertension was reported in 20% of the patients**.** Renal dysfunction was seen in 30% and 47% of patients in these studies while in our study not a single patient developed renal dysfunction. One reason for this major difference in the side effect profile may be due to low dose of cyclosporine used. Following international guidelines the lowest effective dose was used in our study to reduce toxicity to acceptable levels[26].

Yet another explanation could be the difference in the patients group and the smaller sample size of our study population. Hypertrichosis, gingival hyperplasia and gastrointestinal side effects were also less in number as compared to other studies quoted above.

The limitation of the study included non availability of the control group and base line record.

CONCLUSION

Patients can tolerate and can show improvement in early active and potentially disabling Rheumatoid Arthritis.

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