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ORIGINAL ARTICLE

Cyclosporine in Resistant Systemic Arthritis - A Cheaper Alternative to Biologics

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Abstract

Objectives To assess the efficacy of cyclosporine (CsA) in patients of oral steroid unresponsive or steroid dependent systemic juvenile idiopathic arthritis (sJIA); to evaluate the optimum dosage and blood level of CsA to achieve and maintain remission and to observe for side-effects on prolonged usage.

Methods This prospective observational study was conducted on children with steroid dependent /refractory sJIA admitted at the Institute of Child Health, Kolkata from July 2009 through November 2014. A total of 82 sJIA was diagnosed; 15 were steroid dependent /refractory and were included as candidates for cyclosporine therapy.

Results CsA was used in 15 patients; 13 showed a favourable response with significant steroid sparing effect and minimal toxicity.

Conclusion CsA was found to be effective in almost 75% of frequently relapsing steroid dependent sJIA to achieve and maintain remission. The average cost of therapy for a 20 kg patient on CsA was found to be 10,000 INR (132 EURO)/ patient over a 6 mo period; which would amount to 100,000 INR (1318 EURO)/patient with Tocilizumab for the same duration.

Keywords Systemic arthritis · Cyclosporine · Systemic juvenile idiopathic arthritis treatment

Introduction

Systemic juvenile idiopathic arthritis (sJIA) is usually responsive to corticosteroids although prolonged usage is associated with significant toxicity [1, 2]. Other disease modifying anti rheumatic drugs (DMARDs) have been tried, but with limited success [1, 2]. The biologic agents (Anakinra, Tocilizumab) are promising [1, 3–5], but in a developing country like India, their usage is limited because of availability issues (Anakinra) and prohibitive costs. Cyclosporine (CsA) is a potent immunosuppressive agent being used successfully in many autoimmune disorders. Although previous experiences have shown a mixed response to its usage in sJIA [6, 7], keeping in mind the cost-benefit, authors started using CsA in steroid dependent/ refractory sJIA patients, who frequently relapsed with predominant systemic symptoms. Here authors present a series of 13 cases of frequently relapsing, steroid dependent sJIA who showed favourable response to CsA.

Objectives of the present study were to assess the efficacy of CsA in patients of oral steroid unresponsive or steroid dependent sJIA. Patients who had recrudescence of systemic symptoms on transition from intravenous to oral steroids were labelled as unresponsive, and those patients who relapsed on tapering of steroids below 0.5 mg/kg/d formed the steroid dependent group.

Efficacy was judged clinically by fever defervescence, absence of rash and arthritis, and maintenance of the afebrile state even on gradual tapering/ withdrawal of steroid, together with improvement of the laboratory inflammatory markers *i.e.,* increase of hemoglobin and decrease in erythrocyte sedimentation rate (ESR), C-reactive protein (CRP).

The other objectiives were to evaluate the optimum dosage and blood level of CsA to achieve and maintain remission and to observe for side-effects on prolonged usage.

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Material and Methods

Clinical records of children fulfilling the 1995 ILAR diagnostic criteria of sJIA admitted at the Institute of Child Health, Kolkata during the time period July 2009 through November 2014 were reviewed. The diagnosis of sJIA was based on the ILAR criteria and exclusion of other diseases. Details of clinical and laboratory features, treatment and outcome were noted. A total of 82 sJIA patients were diagnosed during the study period. Fifteen were steroid dependent /refractory and were included as candidates for cyclosporine therapy. As per standard therapy of sJIA prior to addition of CsA, all patients were started on subcutaneous methotrexate at 15 mg/m^2/wk as a steroid sparing disease modifying agent.

Criteria for initiating cyclosporine was repeated flares (3 or more times) on stopping or attempting to taper off steroids (<0.5 mg/kg/d), in spite of being on methotrexate.

Monitoring involved: Clinical – Any systemic symptoms (fever, rash, organomegaly), number of joints involved, blood pressure, hypertrichosis, opportunistic infections and Lab parameters included complete blood count (CBC), creatinine, ESR, CRP and SGPT.

These were evaluated initially 2 wkly X 1 mo; then monthly X 3 mo and subsequently 3 monthly.

Cyclosporine blood level was initially done after 96 h of starting treatment, then depending upon the response, usually every 4 monthly.

The following parameters have been considered when evaluating CsA efficacy in sJIA [6, 7]:

Clinical Parameters

i) Absence of fever
ii) Improvement of joint symptoms (absence of arthritis or minimal 50% reduction in number of active joints or pain by physician's global assessment)
iii) Absence of rash

Laboratory Parameters

i) Reduction of ESR and CRP (normalisation or at least 70% reduction from initial values)
ii) Increase in hemoglobin (at least 1 g/dl), diminution of absolute neutrophil count by atleast 50%.

Corticosteroid Sparing Effect

Decrement of daily dose by atleast 50% from baseline for maintenance of remission.

Besides all these, a global clinical evaluation was also performed.

The patients were reviewed after 2 wk, then monthly × 3 mo, 6 mo, 9 mo and 12 mo of starting CsA. They were labelled as responders when any 2 of the clinical parameters plus both the laboratory parameters along with steroid sparing effect was observed.

CsA tapering was started when a patient was in both clinical and biochemical remission for at least 6 mo.

Results

CsA was used in 15 patients over a time period of 5 y and the average starting dose was 3.1 mg/kg/d (range 1.9 to 4).

Of these, 13 responded to CsA and 2 did not respond.

Of the 13 responders, 11 became afebrile within 2 wk of initiation of CsA, the remaining 2 within a mo. Two patients relapsed at 10 and 14 mo while on CsA, but could be managed with a short course of steroid. Remaining 11 never relapsed after initiation of CsA. So a permanent remission rate of 73% was achieved with a mean follow up of 3.9 y (range 9 mo to 6 y) after starting CsA. The rash disappeared along with fever in 10 patients, 3 continued to have rashes which subsided after 3 to 8 mo of therapy.

Though most of present patients had predominant systemic features, articular symptoms were found to be less responsive, 5 had arthritis at cyclosporine initiation. At the end of 3 mo, 3 had persistent arthritis and needed additional drugs like leflunomide or intraarticular steroid.

Seventy percent reduction of ESR and CRP was noted in 11 patients at the end of 2 wk; and at 1 mo they normalised in all 13 responders.

Improvement in hemoglobin by 1 g/dl from the baseline was seen in 4 patients at the end of 1 mo, and remaining at 3 mo.

Depending on response, steroid tapering was mostly started after 1 mo of CsA and could be completely withdrawn after a mean duration of 6.15 mo of starting CsA. Before starting CsA these children had frequent relapses with the average rate of relapse being 3.4 times/patient, required frequent steroid administration and the mean duration of steroid treatment was 14 mo/patient. The authors were able to reduce the dose of steroid by 50% after a mean duration of 2.4 mo of CsA initiation. This 50% reduction of steroid dosage could be achieved in 8 patients at the end of 2 mo and all 13 at the end of 3 mo. Three patients needed a very low dose steroid (0.2–0.4 mg/kg/d of Prednisolone) along with CsA for a prolonged period up to 6 mo to maintain the remission. However even this low dose steroid could be subsequently weaned off (Table 1).

The physician's global evaluation was good in 9 patients, moderate in 4 patients and poor in 2 patients after the end of 1 mo therapy.

Of the 13 children who responded, CsA could be tapered and stopped in all after a mean duration of 20 mo (range 16 to

Table 1 Response pattern of 13 patients who responded to cyclosporine therapy

	2 wk	1 mo	3 mo	6 mo	9 mo	12 mo
Defervescence	11	13	13	13	13	13
Improvement in joint symptoms (n = 5)	0	1	2	4 (After Leflunomide)	4 (After Leflunomide)	5 (After Leflunomide + intraarticular steroid)
70% reduction of ESR and CRP	11	13	13	13	13	13
Increase in Hb by 1 g % from baseline	0	4	13	13	13	13
Decrement of the dose of steroid by 50%	0	3	10	13	13	13

24 mo). The mean follow-up from the onset of therapy is 3.9 y (range 9 mo to 6 y).

Two patients who failed to respond to CsA received biologics (Tocilizumab).

So, to sum up ($n = 15$), i) off Steroid, off CsA patients were 13 (11 never relapsed, 2 relapsed but responded to short course steroids); ii) patients who did not respond to CsA were 2 and iii) the mean dose of CsA to achieve the remission was 3.9 mg/kg/d (Fig. 1).

The mean blood level in which remission was induced was 138.4 ng/ml. There was no significant side-effect noted except hirsuitism in one and transient hypertension in another which subsided on tapering of CsA.

The average cost of therapy for a 20 kg patient on CsA was found to be 10,000 INR (132 EURO)/ patient over a 6 mo period *i.e.*, around 1700 INR(22 Euro)/mo.

Discussion

sJIA is a clinical entity distinguished from other types of arthritis by its predominant systemic features and the potential for involving various organs. Though the exact mechanism of these florid systemic manifestations is not clearly known, presently it is evident that there is a predominant role of different cytokines like IL1 and IL6. The therapeutic approaches remain difficult due to florid and overwhelming systemic manifestations as well as the predilection for evolution to chronic erosive polyarthritis. Hence, the efficacy of drug therapy in systemic JIA is particularly difficult to evaluate because of the variability in course and outcome of the disease. The disease may be predominantly arthritic, with minimal and easily controllable systemic features, or may be predominantly systemic, with minimal and easily controllable arthritis. Glucocorticoids have excellent effectiveness against both the manifestations and are almost always effective in inducing remission, but toxicity limits their long term administration.

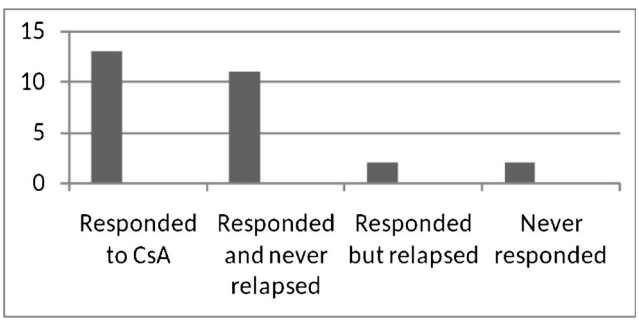

Fig. 1 Response pattern of the 15 patients initiated on cyclosporine

Researchers have been looking for an ideal steroid sparing drug that may be used safely in sJIA with acceptable side-effects profile. Pediatric rheumatologists started using CsA as a steroid sparing agent in sJIA in the early 90s; influenced by a few reports from adult literature which were published as isolated case reports and case series [8–10]. However CsA usage in sJIA never attained popularity and in most published literature the result was not encouraging. Even the ACR 2011 guidelines stated that effectiveness of initiation of calcineurin inhibitors for patients with active fever without active arthritis was uncertain for initial management [1].

In a developing country like India although a large number of refractory sJIA patients are encountered, the access to biologics remain prohibitive mainly due to financial constrains. Since there are no trials from India about CsA usage in refractory sJIA, an endeavour was made to revaluate its efficacy in long time usage in difficult sJIA. Authors' open label prospective study was the first of its kind from India wherein little information is available on its usage, either as monotherapy or in combination with other second-line agents, and no controlled studies exists.

Ostensen et al. [11] reported temporary symptomatic effects on disease activity in 14 patients who received CsA at doses of 4–15 mg/kg/d for 6–20 mo. Eleven of the 14 patients discontinued treatment either due to lack of efficacy ($n = 4$) or side-effects ($n = 7$). The most common side-effects were hypertrichosis, an increase in serum creatinine or potassium, and a decrease in hemoglobin. In contrast, the side-effect profile in present study was almost negligible, possibly because of the mean lower dosage used.

The efficacy and safety of CsA at the mean dose of 5 mg/kg/d was investigated by Pistoia et al. [12] in 9 patients treated for 9–23 mo. Significant improvement in joint inflammation and reduction of steroid dose were observed. The drug

was well tolerated in all patients and no elevation of serum creatinine was detected; side-effects included mild hypertension, hypertrichosis, hypoproteinemia, tremors, and alopecia. In present cohort, though arthritis failed to show a remarkable response, but systemic symptoms along with reduction of inflammatory markers by 70% was seen in almost 80% of present patients (Table 1).

One of the largest trial of using CsA in 34 patients of sJIA was done by Gerolini et al. in Italy [7] and they concluded that it may be used in some cases but only a minority of the patients achieved total remission and almost 25% discontinued the drug due to side-effects. However, in present study there was a permanent remission of almost 73% with a minimal side-effect profile.

To authors' knowledge, only two studies reported the results of the combined administration of MTX and CsA in sJIA [13, 14]. Reiff et al. [15] evaluated retrospectively the efficacy and safety of the combined administration of MTX and CsA in 12 patients with JIA who were refractory to a combination of NSAIDs, high doses of prednisone, and/or MTX. At the end of the treatment period there was a reduction in the mean number of swollen joints from 20.6 to 10.8 and an increase in the mean level of hemoglobin from 10.8 to 11.0 g/dl; the number of patients with fever and morning stiffness decreased from 8 to 1 and from 10 to 5, respectively; both the group of patients continued taking prednisone but the average prednisone dose considerably diminished. The authors also observed the similar steroid sparing effect and decrement of the total dose of prednisolone by 50% in 53% patients at the end of 2.4 mo and 86% at the end of 3 mo therapy (Table 1).

Ravelli et al. [13] reported encouraging results with CsA in 17 patients who were refractory to MTX as monotherapy. At the end of the combination treatment period (6–30 mo, median 10 mo), 8 patients (47%) met the ACR Pediatric 30 definition of improvement in JIA; 5 patients (29%) met the 70% definition of improvement, and 2 patients (12%) achieved complete disease control. Seven patients (41%) experienced side-effects: 4 had gastrointestinal discomfort, 1 liver transaminase elevation, and 2 ≥ 30% increase in the serum creatinine concentration. No patient discontinued combination therapy due to side-effects.

Results of the PRCSG/PRINTO phase IV post marketing surveillance study suggested that CsA may have a lesser efficacy profile than MTX or etanercept, the frequency of side-effects may be similar [6].

Though most previous studies reveal a less than satisfactory efficacy of CsA, present study contrasts all of them by a permanent remission rate of 73%. The authors have used it in 15 patients of chronic frequently relapsing form of disease wherein 13 went into remission and CsA could be tapered and stopped in all after a mean duration of 20 mo. The systemic symptoms like fever and high inflammatory markers were more responsive than the articular symptoms.

The most significant response was found in terms of reducing or stopping the use of steroid. The dosage of steroid could be reduced by 50% after a mean duration of 2.4 mo and steroid could be completely withdrawn in these 13 patients after a mean duration of 6.15 mo of starting CSA. The efficacy of achieving and maintaining the biochemical remission in terms of reduction of ESR, CRP and TLC and increase of hemoglobin was also satisfactory.

Unlike the other series; the side-effects profile had been minimal with hirsuitism in one and transient hypertension in another.

The authors acknowledge the many limitations including the non-controlled, observational design. The case report format was designed to collect only the essential information; authors did not obtain more detailed data, such as the ACR pediatric 30 response rate.

Conclusions

CsA was found to be effective in achieving and maintaining remission in almost 75% of frequently relapsing steroid dependent sJIA. The systemic symptoms like fever and rash responded far better than the articular symptoms.

The average cost of therapy for a 20 kg patient on CsA was found to be 10,000 INR (132 EURO)/ patient over a 6 mo period; which would amount to 100,000 INR (1318 EURO)/ patient with Tocilizumab for the same duration.

To conclude, in patients with resistant systemic JIA who relapsed frequently with systemic symptoms, CSA was found to be a cheaper alternative to biologics in inducing and maintaining remission without producing significant side-effects.

Authors' Contribution PP conceptualised the project. Both PP and PPG were involved in patient management and data collection. All three authors drafted the manuscript. Prof. Apurba Ghosh, Director, Institute of Child Health, Kolkata will act as guarantor for this paper.

Compliance with Ethical Standards

Conflict of Interest None

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