Cyclosporine A in juvenile idiopathic arthritis. Results of the PRCSG/PRINTO phase IV post marketing surveillance study

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Abstract

Objective

To investigate the clinical use patterns, clinical effect and safety of cyclosporine A (CSA) in juvenile idiopathic arthritis (JIA) in the setting of routine clinical care.

Methods

An open-ended, phase IV post marketing surveillance study was conducted among members of the Pediatric Rheumatology Collaborative Study Group (PRCSG) and of the Paediatric Rheumatology International Trials Organisation (PRINTO) to identify patients with polyarticular course JIA who had received CSA during the course of their disease.

Results

A total of 329 patients, half of whom had systemic JIA, were collected in 21 countries. Data were collected during 1240 routine clinic visits. CSA was started at a mean of 5.8 years after disease onset and was given at a mean dose of 3.4 mg/kg/day. The drug was administered in combination with MTX in 61% and along with prednisone in 65% of the patients who were still receiving CSA. Among patients who were still receiving CSA therapy at the last reported visit, remission was documented in 9% of the patients, whereas in 61% of the patients the disease activity was rated as moderate or severe. The most frequent reason for discontinuation of CSA was insufficient therapeutic effect (61% of the patients); only 10% of the patients stopped CSA because of remission. In 17% of the patients, side effects of therapy was given as the primary reason for discontinuation.

Conclusion

This survey suggests that CSA may have a less favourable efficacy profile than MTX and etanercept, whereas the frequency of side effects may be similar. The exact place of CSA in the treatment of JIA can only be established via controlled clinical trial.

Key words

Juvenile idiopathic arthritis, juvenile rheumatoid arthritis, juvenile chronic arthritis, cyclosporine A, methotrexate, cyclosporine, combination therapy.

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Introduction

Juvenile idiopathic idiopathic arthritis (JIA) is the most common chronic rheumatic disease in childhood (1), and is one of the leading causes of acquired disability in the pediatric age group (2, 3). Initial treatment for JIA typically includes non-steroidal- anti-inflammatory drugs (NSAIDs) or, in patients with involvement of one or few large joints, intra-articular long-acting corticosteroid injections. A significant proportion of patients, however, do not achieve adequate disease control with first-line therapies alone. These patients are candidate for a more aggressive approach with second-line agents.

Methotrexate (MTX) is currently the therapeutic agent of choice for patients with JIA, particularly with the polyarticular and systemic subtypes, who fail to respond to NSAIDs or require systemic corticosteroid administration to control disease activity (4). A number of non-controlled studies and a placebo-controlled trial have shown that MTX is effective and well tolerated in children with JIA, with 60 to 70% of them experiencing a significant clinical benefit at the standard dose of 10 mg/m^2/week (5). Furthermore, preliminary evidence suggests that this drug may significantly alter the natural history of the disease (6, 7). However, 30-40% of patients do not show a satisfactory response to MTX given at the standard doses. This group includes most of the patients who are at risk of developing irreversible joint damage and permanent disability. Several different therapeutic approaches have been proposed for these patients, including the parenteral administration of higher doses of MTX, with a plateau efficacy at about 15 mg/m^2 (8), the use (alone or in combination with MTX) of other second-line agents, such as sulfasalazine (9), cyclosporine A (CSA), azathioprine, or leflunomide (10), and, more recently, the administration of the biologic agents (11-13). In the most severe and recalcitrant cases, autologous stem cell transplantation has been considered (14).

Although the use of CSA, as monotherapy or in combination with MTX, has been used in clinical practice in many pediatric rheumatology centers, only a limited and anecdotal information exists about its efficacy and safety profile in patients with JIA (15-19). This contrasts with numerous studies, including controlled trials, which have established the place of this medication in the management of adult patients with rheumatoid arthritis (20-23). Obtaining further insights into the role of CSA in JIA is important in the process of exploring alternative therapies for patients who do not respond or are intolerant to MTX, and in providing advice to pediatric rheumatologists who work in countries in which the biologic agents are not widely available.

For these reasons, the Pediatric Rheumatology Collaborative Study Group (PRCSG) (5, 11, 24) and the Paediatric Rheumatology International Trials Organisation (PRINTO), (8, 25) conducted a phase IV post marketing surveillance study to describe the clinical use patterns, clinical effect, and short, intermediate and long-term safety of CSA in the setting of daily care of patients with JIA.

Patients and methods

Study setting

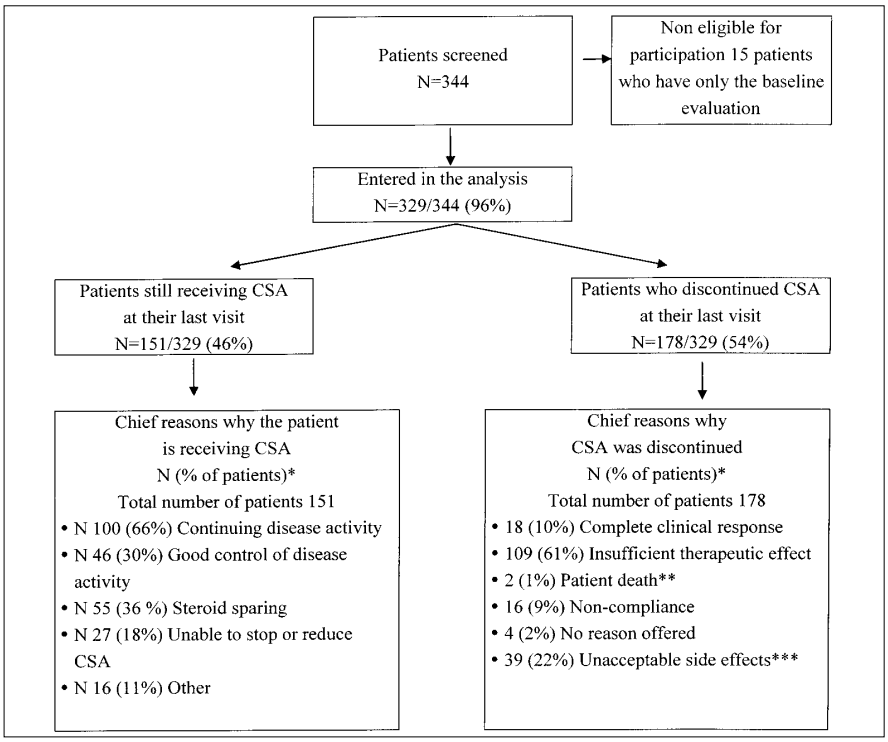
The PRCSG based in North America and PRINTO whose memberships extends to 47 countries, are international complementary networks whose goal is to promote, facilitate and conduct high quality research in the field of pediatric rheumatology. All active members (mainly pediatric rheumatology tertiary care centers) who are part of the two networks were invited to participate in the survey.

Study design and patient selection

The study was designed as an open, observational survey. Participating physicians were asked to identify all patients with a diagnosis of JIA according to the Edmonton criteria (26, 27) or juvenile rheumatoid arthritis (JRA) (28) who had a polyarticular course, were followed between January, 1988 and May, 2003, and had received CSA for any duration during the course of their illness. Since most of the participating centers used the term JIA to classify their patients, for the remaining children classified as JRA, re-

assignment to JIA subtype (from USA) for patients was done centrally using the information available on the CRF forms. Data collection was conducted retrospectively by reviewing the clinical charts of patients who had received CSA before the study initiation, and prospectively by recording the clinical data of patients who took CSA after study initiation. In the latter patient group, the study purposes were explained to the patient or the parent/-legal guardian, as appropriate, and a verbal informed consent was sought at the first visit. No blood specimens were required specifically for the purposes of the study.

A single page data collection form was used composed of two parts: the first part included demographic data and information regarding JIA onset type and current doses of CSA, MTX, prednisone, and NSAIDs that the patient was receiving at the time of form completion. In the second part, a flow diagram divided the patients in two arms depending on whether they were still receiving or had been discontinued from CSA. For patients who were still on CSA, the examining physicians were asked to indicate the chief reasons why the patient was receiving the drug, to provide the values of the last available serum creatinine and blood pressure and to rate the current level of the patient's disease activity (complete clinical response, mild activity, moderate activity, or severe activity). Information requested for patients who were discontinued from CSA included reason(s) for treatment withdrawal, patient's clinical course following discontinuation of CSA, values of last available serum creatinine and blood pressure, and rating of the current level of the patient's disease activity. Participating physicians were instructed to complete the data collection form at visits occurring at about 6 month intervals or at any other time if a clinical event occurred that they felt was worth reporting. The PRCSG collected data via fax or mail from North America, whereas study participants mainly in Europe and Latin America sent their forms to PRINTO. Query resolution was conducted by the PRCSG and PRINTO Coordinating Centers.



*N and % do not add up to 100 because more than one reason can be stated.
**2 deaths reported, 1 patients due to with vasculopathy and the second 1 due to for myocarditis; neither death was related to CSA.
***31 pts listed unacceptable AEs as the primary reason for discontinuation.

Fig. 1. Flow diagram of the patients enrolled in the study.

Statistics

Descriptive statistics (means, frequencies) were used for reporting demographics, clinical characteristics, efficacy variables, and side effects. Data were stored and analyzed using Excel XP (Microsoft).

Results

Figure 1 illustrates the flow diagram of the study patients. A total of 344 patients were enrolled in the following 21 countries: Argentina (8), Brazil (17), Czech Republic (2), Denmark (18), France (10), Germany (39), Greece (30), Hungary (9), Israel (5), Italy (72), Netherlands (8), New Zealand (1), Norway (3), Portugal (3), Slovakia (9), Spain (5), Sweden (2), Switzerland (5), Turkey (2), United Kingdom (11), USA (85). Of the 344 study patients, 85 (25%) were enrolled by the PRCSG centers and 259 (75%) by the PRINTO network. Table I shows the baseline characteristics of the patient population. Since there were no differences in the baseline demographic and disease characteristics of PRCSG's and PRINTO's patients (data not shown), results are reported for the combined datasets from the two networks. It is worth noting that more than half of the patients enrolled had systemic JIA, which evolved into a polyarticular course.

Fifteen (4%) of the 344 patients were excluded from the analysis because they had only the baseline evaluation (Fig. 1). The remaining 329 patients had a total of 1240 visits recorded: 713 visits (58%) were recorded from patients who were receiving CSA at that the time of the visit; 527 visits (42%) were recorded after the patient had discontinued CSA. At the time of their last reported visit, 151 patients (46%) were receiving CSA and 178 (54%) had discontinued the drug.

CSA therapy and concomitant medications

Therapy with CSA was started at at a

mean of 5.8 years after disease onset (Table I). The treatment duration (time lapse from initiation of CSA therapy to date of last visit reported or date of discontinuation) was < 6 months in 74 (23%) patients, 6 to 12 months in 54 (16%) patients, 12 to 24 months in 88 (27%), and more than 2 years in 113 (34%). The mean treatment duration was 1.8 years (SD 1.7) in the 151 patients who were still receiving the drug at their last reported visits, and 1.7 years (SD 1.5) in the 178 patients who had discontinued the drug. The mean dose of CSA across all study visits was 3.4 mg/kg/day. CSA was administered in combination with MTX (mean dose, 0.5 mg/kg/week or 15 mg/m^2/week) in 92 (61%) of the 151 patients who were still receiving CSA. The concurrent administration of prednisone (mean dose, 8.7 mg/day), was reported in 98 (65%) patients who were still receiving CSA.

Table I. Baseline characteristics of the 344 study subjects.

Baseline characteristics	Sample (N = 344)
Age at start of CSA, mean ± SD, in years	11.1 (5.5)
Disease duration at start of CSA, mean ± SD, in years	5.8 (6.8)
Disease subtype, no. (%)	
Systemic arthritis	185 (54%)
Polyarthritis	112 (32%)
Oligoarthritis extended	44 (13%)
Other	3 (1%)

Table II. Physician's global rating of disease activity in the patients who were still receiving CSA therapy at the last reported visit.

	Systemic arthritis N = 76	Poly-arthritis N = 44	Oligoarthritis extended N = 28	Other N = 3	Total N =151
Complete clinical response*	4 (5%)	3 (7%)	5 (18%)	1 (33%)	13 (9%)
Mild activity	23 (30%)	12 (27%)	8 (29%)	2 (67%)	45 (30%)
Moderate activity	25 (33%)	26 (59%)	10 (35%)		61 (40%)
Severe, uncontrolled disease activity	24 (32%)	3 (7%)	5 (18%)		32 (21%)

*Complete clinical response is the same as clinical remission, except that the patient is still receiving drug treatment.

Efficacy

Table II reports the physician's global rating of disease activity in the patients who were still receiving CSA therapy at the last reported visit divided according to the JIA disease subtype. A complete clinical response (i.e. inactive disease) was documented in 13 patients (9%); the disease activity was rated as moderate or severe in 93 patients (61%). Children with systemic JIA tend to have a more severe, uncontrolled disease when compared to the other subtypes, while children with polyarthritis tend to have a better control. As shown in Figure 1, the chief reason why 151 patients (713 visits) were still receiving CSA at the last follow-up visit was the presence of continuing disease activity (66% of the patients). The main reason listed in the 178 patients who had discontinued CSA was the insufficient therapeutic effect (61% of the patients); 39 of the 178 patients (22%) listed side effects as one of the reasons for the discontinuation of CSA (see below); 10% of the patients stopped CSA because of the achievement of complete clinical response. The frequency of CSA discontinuation was higher in patients with the systemic (101/185, 55%) and polyarthritis (60/112, 54%) subtypes than in those with the extended oligoarthritis subtype (14/44, 32%). Table III shows the clinical course and side effects following discontinuation of CSA. In 78 patients (44%), there was only a small change in the overall clinical status; 49 (28%) patients began anti-TNF therapy and 34 (19%) patients experienced a decrease in disease activity. Twenty (11%) patients had prompt resolution of side effects after discontinuation of CSA.

Safety

The mean systolic and diastolic pressure documented in the study visits were 108 (SD 26) and 64 (SD 17) mm Hg, respectively; values of systolic and diastolic pressure greater than 140 and 90 mm Hg, respectively, were recorded in only 2% of the visits. The mean serum creatinine level was 0.6 mg/dL (SD 0.2), values greater than 0.8 and 1 mg/dl dL were detected in 13% and 4% of the visits, respectively. There were 2 deaths, 1 due to vasculopathy and 1 to myocarditis; both were unrelated to CSA. Table IV shows the list of side effects that led to discontinuation of CSA in 39/178 (22%) patients. In 31 of these patients, side effects of CSA therapy were reported as the primary reason for discontinuation.

Discussion

CSA is a potent immunomodulatory agent which inhibits primarily the cellular production of cytokines, predominantly interleukin-2, involved in the regulation of T-cell activation (29). In adult patients with rheumatoid arthritis (adult RA), CSA as monotherapy has been shown to be an effective treatment (20). Furthermore, the combination of CSA and MTX has been shown in clinical trials to be an effective therapeutic strategy for patients with adult RA whose disease is not controlled by MTX alone (21, 22). However, the potential for irreversible toxicity remains a major concern with the long-term use of CSA in adults (30).

Little information is available on the use of CSA, either as monotherapy or in combination with other second-line agents, in JIA, and no controlled studies exist. Reports on the efficacy of CSA as a single agent for the treatment of JIA have not been too encouraging. Ostensen *et al.* (15) reported temporary symptomatic effects on disease activity in 14 patients who received the drug at doses of 4-15 mg/kg/day for 6-20 months. Eleven of the 14 patients dis-

Table III. Clinical course and side effects following discontinuation of cyclosporine A in the 178 children who had discontinued the drug at the last available study visit.

	N (% of patients)*
Clinical course	
Immediate flare	16 (9%)
Slow but definite worsening	16 (9%)
Little change in overall clinical picture	78 (44%)
Decrease in disease activity	34 (19%)
Began anti-TNF therapy	49 (28%)
Other (i.e. remission, moved)	18 (10%)
Unknown	7 (4%)
Side effects:	
Prompt resolution of side effects	20 (11%)
Slow resolution of side effects	7 (4%)
Persistent side effects	2 (1%)

*More than 1 response is possible. Therefore percents do not add up to 100%.

Table IV. List of side effects categorized as primary or secondary reasons for the discontinuation of CSA in the 39 patients who discontinued the drug due to side effects.

Side effects	No. of patients (%)
Hypertrichosis	7 (18%)
Increased creatinine	6 (15%)
Hypertension	6 (15%)
Gastrointestinal side effects	6 (15%)
Gingival hyperplasia	3 (8%)
Thrombocytopenia	2 (5%)
Seizures	2 (5%)
Other reasons	7 (19%)

continued the treatment either due to lack of efficacy (n = 4) or side effects (n = 7). The most common side effects were hyperthrichosis, serum creatinine or potassium increase, and hemoglobin decrease. The efficacy and safety of CSA at the mean dose of 5 mg/kg/day were investigated by Pistoia *et al.* (16) in 9 patients treated for 9-23 months. 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, hyperthrichosis, hypoproteinemia, tremors, and alopecia. In an open prospective study of 41 patients, 34 of whom had systemic disease and the remaining JIA-associated chronic anterior uveitis, Gerloni *et al.* (18) reported a satisfactory decrease in fever and reduction of corticosteroid dose. The benefits on arthritis symptoms, laboratory parameters, and uveitis activity were less clear-cut. Side effects were frequent, but were usually mild or reversible. The most frequent of them was an increase in serum creatinine > 30%, which was observed in 16 patients (39%). Six patients (15%) developed hypertension. Other common side effects were hypertrichosis (29%) and gum hypertrophy (12%). Sixty-six percent of the patients were withdrawn from therapy because of inefficacy or toxicity; however 8 systemic patients with systemic illness discontinued CSA due to disease remission. The CSA dose was 3-5 mg/kg/day and the average treatment duration was 1.4 years.

To our knowledge, only two studies reported the results of the combined administration of MTX and CSA in JIA. Reiff *et al.* (17) 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. Therapy with MTX and CSA was given for a mean of 17.7 months (range 6-32 months). The mean initial/final doses of MTX and CSA were 14.5/16.1 mg/week and 3.7/3.3 mg/kg/day, respectively. 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 was decreased from 8 to 1 and from 10 to 5, respectively; both the number of patients taking prednisone and the average prednisone dose were considerably diminished. CSA was well tolerated in the majority of patients. However, 7 of the 12 children treated with both MTX and CSA experienced a rise in serum creatinine of at least 0.2 mg/dl, although none developed abnormal creatinine levels during the follow-up period. Ravelli *et al.* (19) 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 months, median 10 months), 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 increase ≥ 30% in the serum creatinine concentration. No patient discontinued combination therapy due to side effects.

In this survey, we investigated the efficacy and safety profile of CSA in a large sample of patients with JIA who received the drug in the setting of routine clinical care. More than half of the patients enrolled had the systemic subtype, perhaps reflecting the apparently distinctive effect on the fever and the corticosteroid-sparing potential observed in some of the above studies. On average, CSA was started very late in the course of the disease (presumably after the failure of several other therapeutic regimens), which may partially explain the suboptimal efficacy results. The mean dosage of about 3.4 mg/kg/day is in the range of that recommended in the international guidelines (31), although a wide variability was seen. In the majority of patients,

CSA was given together with MTX and/or prednisone, again suggesting that most patients had long-standing, refractory disease.

The overall efficacy profile of CSA was less than satisfactory. Among patients who were still receiving the drug at the last follow-up evaluation, the clinical response was judged by the attending physician as complete in only 9% of the patients, whereas in 61% of the patients the disease activity was rated as moderate or severe. Furthermore, the main reason listed in patients who were discontinued from CSA was the insufficient therapeutic effect and only 10% of the patients stopped the treatment due to clinical remission. The side effects reported most frequently were those that are commonly seen with the use of CSA and included hyperthrichosis, increased serum creatinine levels, hypertension, gastrointestinal discomfort, and gingival hyperplasia. In 22% of the patients, side effects were the primary reason for discontinuation of treatment. Overall, less than half of the patients were still receiving the drug at the last follow-up visit, after a mean of 1.7 years of therapy. The rate of treatment discontinuation due to side effects were comparable to observed with MTX monotherapy or etanercept (8, 11, 32-34), whereas the long-term retention rate may compare less favourably with the clinical experience with MTX and biologic agents.

We acknowledge the many study limitations including the non-controlled, observational design, and the largely retrospective nature of data collection. Furthermore, since the case report form was designed to collect only the essential information, we did not obtain more detailed data, such as the ACR pediatric 30 response rate (35-37), the blood pressure values adjusted for age, the serum creatinine levels standardized according to age and to the reference intervals of each laboratory, the rheumatoid factory positivity, psoriasis and extra-articular manifestations, and the specific effect of CSA on JIA systemic features and uveitis. A more reliable evaluation of the efficacy and safety of CSA in JIA would require a randomized controlled study. Notably, in an international survey conducted in 1996 (38) among pediatric rheumatologists, a controlled trial comparing CSA and MTX was indicated as the most important study to be performed.

In conclusion, our survey suggests that CSA may have a less favourable efficacy profile and long-term retention rate than MTX or etanercept, whereas the frequency of side effects may be comparable. The exact place of CSA in the treatment of JIA can only be established via a randomized controlled trial.

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