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Efficacy and safety profile of cyclosporin A in the treatment of juvenile chronic (idiopathic) arthritis. Results of a 10-year prospective study

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Abstract

Objective. This open prospective trial was performed in order to assess the efficacy and safety of cyclosporin A in the treatment of patients with juvenile chronic arthritis (JCA).

Methods. Thirty-four of the patients enrolled were affected by systemic-onset disease and seven by chronic anterior uveitis associated with JCA. The cyclosporin dose was usually 3–5 mg/kg per day. The average duration of therapy was 1.4 yr, with a maximum of 7.2 yr.

Results. The efficacy of treatment was mainly evident in terms of control of fever and reduction of steroid therapy. The benefits with respect to arthritis, laboratory parameters and uveitis seemed to be less clear-cut. Side-effects were frequent but usually mild or reversible. Sixty-six per cent of the study population withdrew from therapy because of inefficacy or side-effects. Eight systemic patients withdrew from therapy owing to complete remission.

Conclusion. Cyclosporin can be used in the treatment of JCA, its main benefits being the control of fever and a steroid-sparing effect.

KEY WORDS: Cyclosporin, Therapy, JCA, Children, Uveitis, Systemic.

Cyclosporin is a non-cytotoxic immunomodulating drug whose immunological selectivity distinguishes it from other immunosuppressants, as its effects are limited to lymphoid cells; it selectively and reversibly inhibits the helper inducer $CD4^+$ T lymphocytes that mediate antibody-dependent and cellular allo- and autoimmune responses [1]. Most of these immunomodulating effects are due to the fact that its inhibition of messenger RNA transcription also inhibits the synthesis of interleukin (IL)-2 and other lymphokines produced by activated T lymphocytes, such as IL-1, tumour necrosis factor (TNF) and α-interferon [2–4].

Twenty years of clinical experience with this drug, which has been used in humans since 1978, has documented its efficacy and safety in the long-term treatment of organ transplantation, and more recently attention has been focused on its use in immunopathological diseases. Specifically, cyclosporin appears to be a rational therapeutic approach to rheumatoid arthritis (RA), the pathogenesis of which seems to be mediated by the activation of T lymphocytes. Many double-blind trials and long-term follow-up studies have described its efficacy and safety in this disease [5–10]. Doses of cyclosporin between 2.5 and 10 mg/kg per day are effective in adult RA, resulting in an improvement in clinical variables, such as joint pain and morning stiffness, and a sparing effect on daily corticosteroid doses. Like others, we have found that cyclosporin is also useful in adult Still's disease [11–13]. Most of the side-effects of cyclosporin are dose-related: doses of up to 5 mg/kg per day seem to be well tolerated, and adverse effects such as hypertension and hyper-creatininaemia are reversible by reducing the dose or by withdrawing the drug.

The therapeutic approach to juvenile chronic arthritis (JCA) is at times very difficult, particularly in systemic-onset disease. Management is often complicated by the difficulty of controlling systemic symptoms (frequently associated with severe anaemia) and of preventing the possible evolution into erosive chronic polyarthritis (50% of cases), which often results in extreme disability. Although the mechanisms causing the clinical features of systemic-onset JCA (high spiking fever, joint inflammation, leucocytosis, thrombocytosis and anaemia) are

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unknown, indirect evidence suggests that cytokines (e.g. IL-1, IL-6, TNF) [14, 15] may play an important pathogenic role. Since it has been shown that cyclosporin inhibits the production of these cytokines *in vitro*, there is a rationale for its use in the active phases of Still's disease.

The chronic anterior uveitis associated with pauciarticular-onset JCA is a challenge, as it may follow a persistent course and lead to severe complications and even blindness [16]. The need to induce disease remission and reduce the daily corticosteroid dose has led to the use of second-line drugs in these cases too. Chlorambucil seems to be one of the most efficacious drugs, but its use is limited by serious adverse effects, such as leukaemia and infertility [17].

No experimental model has yet been discovered which can faithfully reproduce the chronic anterior uveitis of JCA, but animal models for the study of intermediate and posterior uveitis have demonstrated the importance of the T-cell network in their pathogenesis [18], and this supports the usefulness of a drug with predominantly anti-T-cell effects, such as cyclosporin. However, many experiences suggest the efficacy of cyclosporin in the treatment of chronic idiopathic uveitis in man, even in children [19–23].

Little is known about the treatment of JCA with cyclosporin. The results of only four trials have been published so far (including the preliminary results of our own series) [24–28], none of which deals with the treatment of the iridocyclitis associated with JCA. The aim of this open prospective trial was to assess the efficacy and safety of cyclosporin treatment in JCA, particularly in systemic-onset disease and pauciarticular-onset-associated uveitis.

Materials and methods

Patients

To be enrolled, patients had to have normal blood urea nitrogen, serum creatinine and blood pressure values. To date we have enrolled 41 patients with JCA (19 males and 22 females), diagnosed on the basis of the Oslo criteria [29]: 34 patients were suffering from systemic-onset disease, and seven from chronic anterior uveitis, all of which were associated with pauciarticular-onset JCA. The mean age at disease onset was 6.8 yr (range 1–15.8), the mean disease duration was 3.8 yr (range 0.5–11.4) and the mean age at the beginning of therapy was 10.6 yr (range 3.7–18).

The reasons leading to the use of cyclosporin were the persistence of systemic symptoms (fever) and/or steroid dependency in 32 cases, the presence of severe arthritis refractory to other second-line drugs, such as gold salts and methotrexate, in two cases, and chronic anterior uveitis due to pauciarticular-onset JCA in seven cases. More than half of the patients ($n = 22$) had already been treated with one or more disease-modifying anti-rheumatic drugs (DMARDs), with unsatisfactory

results in terms of effectiveness (after at least 6 months of treatment) or safety.

Methods

Cyclosporin (Novartis, Basel, Switzerland) was administered p.o. twice daily at 8 a.m. and 8 p.m., usually after breakfast and supper. Prior treatments with non-steroidal anti-inflammatory drugs (NSAIDs) were continued in all of the patients, but previous therapy with other second-line drugs was maintained in only five cases. Topical uveitis treatment remained unchanged in all cases. The patients underwent a complete clinical evaluation at the beginning of treatment and every 3 months thereafter.

Laboratory tests to evaluate drug tolerability (complete blood count, blood urea nitrogen, creatinine, electrolytes, uric acid, transaminases and urinalysis) were performed weekly for the first 4 weeks and subsequently on a monthly basis. Whole-blood cyclosporin levels were monitored before breakfast 12 h after the last administration. This was carried out initially (during the first 2 yr) using the non-specific monoclonal antibody method, which evaluates both the native molecule and its metabolites (therapeutic range 200–500 ng/ml), and subsequently by using the specific monoclonal antibody method, which evaluates cyclosporin but not its metabolites (therapeutic range 100–200 ng/ml). The dose was reduced by 25% in the event of an increase in blood creatinine exceeding 30% of the baseline value, hypertension, or if the blood cyclosporin level was above the therapeutic range. Any lack of improvement in the altered parameter led to a further 25% dose reduction, and ultimately to the suspension of therapy.

The following parameters were considered when evaluating cyclosporin efficacy in patients with systemic disease: fever (reduction or disappearance), arthritis (at least a 50% reduction in the number of active joints), haemoglobin (Hb) concentration (an increase of at least 1 g/dl) and erythrocyte sedimentation rate (ESR; at least a 50% reduction). A global clinical evaluation was also performed. In the patients with chronic uveitis, the following variables were considered: Tyndall score, indicating the cellularity and protein exudation activity of the anterior chamber, and rated: 0, 1+, 2+, 3+, as judged by an experienced ophthalmologist, and visual acuity (from 0 to 10/10). The corticosteroid-sparing effect (a dose reduction of 50% or more) was also considered in all patients.

Results

The average initial dose for the population as a whole was 4.2 mg/kg per day (range 1.4–8.5), with an average maximum dose of 5.0 mg/kg per day (range 2.3–8.5) and an average maintenance dose of 3.6 mg/kg per day (range 1.2–6.7). The average duration of therapy was 1.4 yr (range 1 week to 7.2 yr), with a mean follow-up from onset of therapy of 4.0 yr for patients with

systemic JCA (range 0.3–8.1) and 2.4 yr for those with JCA-associated uveitis (range 0.8–8.1).

The efficacy of treatment was evident mainly in terms of fever, which was evaluated in 25 patients who completed at least 1 month of therapy. Before the onset of cyclosporin treatment, fever had been present for a period ranging from 1 week to 2 months, but receded in 13 patients (52%), often within a few days; two of the patients experienced a recurrence after cyclosporin had been tapered on account of high creatinine levels. Fever was partially controlled in 10 cases and uncontrolled (persistence after 3 months of therapy) in two cases.

The effect on arthritis was evaluated in 29 systemic patients who presented objective signs of arthritis; five of 34 systemic patients who presented only polyarthralgia and systemic symptoms (spiking fever and typical rash) were excluded from the evaluation. Arthritis improved (a reduction of at least 50% in the number of active joints in comparison with baseline) in 11 of the 29 enrolled patients at the third month of follow-up, in 13 of 28 patients at the sixth month (one patient has not yet completed a 6-month period of therapy), and in 12 of 28 patients after 1 yr of follow-up. A persistent improvement on at least two consecutive occasions was observed in nine of 28 patients (32%) at the third and sixth months, and in 10 of 28 (36%) at the sixth and twelfth months. Four out of 29 patients (14%) were judged to have worsened (an increase of at least 50% in the number of active joints) at the third month, three of 28 (11%) at the sixth month and six of 28 (21%) at the twelfth month.

The physician's global evaluation of the 29 patients was poor in 16 patients (55%), moderate in six (21%) and good in seven (24%).

The laboratory parameters evaluated in the group of 34 patients treated for arthritis and/or systemic symptoms were Hb and ESR. Five patients who were also taking erythropoietin were excluded from the Hb evaluation. Hb improved by at least 1 g/dl in comparison with baseline in seven of 29 enrolled patients at the third month of follow-up, in 10 of 28 patients at the sixth month (one patient had not yet completed a 6-month period of therapy) and in 13 of 28 patients at the twelfth month. The improvement persisted at the third and sixth months in seven of 28 patients (25%) and in 10 of 28 patients (36%) at the sixth and twelfth months. The trend of mean Hb value was towards an improvement, although statistical significance was not achieved (from an average of 9.2 g/dl at the baseline evaluation to 10.1 g/dl at the twelfth month).

Compared with baseline, a reduction of 50% or more in ESR was recorded in seven of 34 enrolled patients at the third month of follow-up, in 12 of 33 patients at the sixth month and in 12 of 33 patients at the twelfth month of follow-up. The improvement persisted in seven of 33 patients (21%) at the third and sixth months and in nine of 33 patients (27%) at the sixth and twelfth months. Mean ESR decreased significantly from a mean baseline value of 93 mm/1st h (range 30–150) to 68 mm/1st h (range 5–140) at the sixth month ($P = 0.01$) and

67 mm/1st h (range 8–127) at the twelfth month ($P = 0.01$).

Figure 1 shows the percentages of patients whose arthritis, Hb and ESR values had improved at 3, 6 and 12 months.

The corticosteroid-sparing effect of cyclosporin therapy was remarkable in some cases. Corticosteroids were interrupted in five of 19 patients (26%) treated for severe polyarthritis and/or systemic symptoms and who completed at least 3 months of therapy, and reduced by 50% or more in a further nine cases (47%). The mean prednisone-equivalent dose was reduced from 0.34 mg/kg per day (range 0.06–1.0) at baseline to 0.14 mg/kg per day (range 0–0.4) at the last evaluation during cyclosporin therapy; this difference was statistically significant ($P = 0.001$). Ten of the patients with systemic JCA were not initially taking corticosteroids: nine had their systemic symptoms controlled by
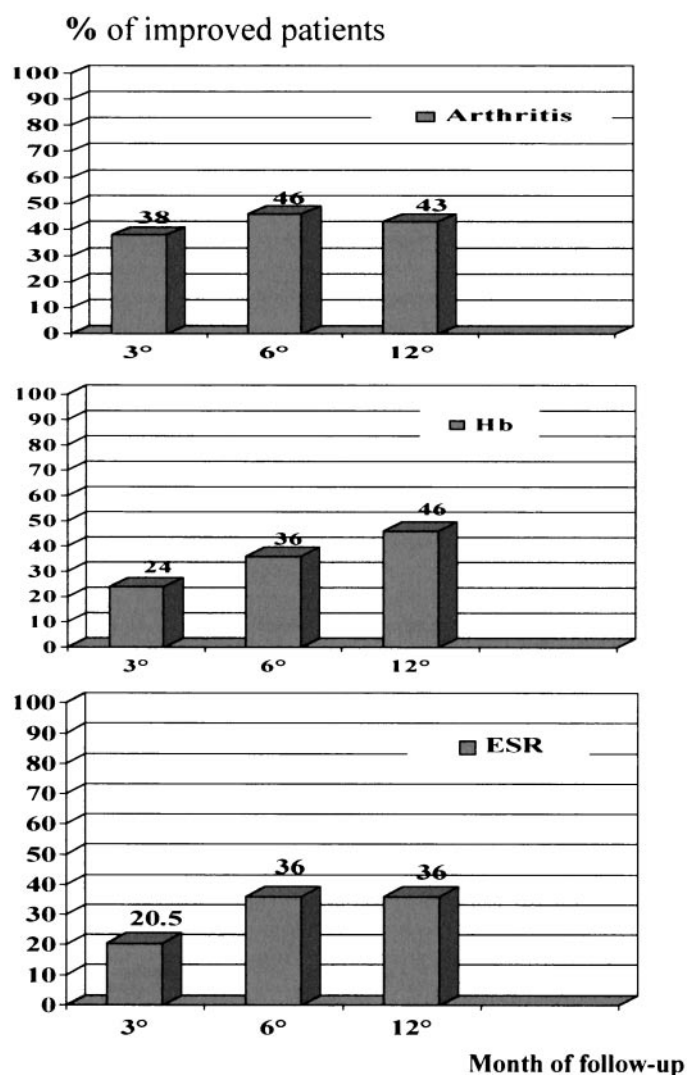

FIG. 1. Percentage of patients who showed improvement in (top) arthritis (more than 50% reduction in number of active joints), (middle) Hb value (increase of at least 1 g/dl), and (bottom) ESR (reduction of at least 50%).

cyclosporin (completely in seven patients, partially in two) and were able to avoid the use of corticosteroids. Cyclosporin failed to control disease activity and corticosteroids needed to be introduced in only one patient.

Two patients with systemic JCA are still on cyclosporin therapy, while the remaining 32 have discontinued treatment. The reasons for drug discontinuation are listed in Table 1.

In the group treated for uveitis, the average maintenance dose of cyclosporin was 4.4 mg/kg per day (range 2.7–6.7). The Tyndall score improved in eight of 12 eyes (66%) and in four of the seven evaluated patients (57%); the mean baseline score of 1.2 (range 1–3) decreased to 0.9 (range 0–3) at the last evaluation. Visual acuity improved in seven of 12 eyes (58%) and in four of the seven evaluated patients (57%); the mean visual acuity of the eyes involved was 5.1 at baseline (range 1–10) and 6.8 (range 3–10) at the last evaluation. This improvement was statistically significant ($P = 0.01$). In no case was it possible to discontinue corticosteroid therapy; the dose was reduced in four patients and increased in two. However, the mean prednisone-equivalent dose was reduced from 0.41 mg/kg per day (range 0.05–0.9) at baseline to 0.26 mg/kg per day (range 0.06–0.7) at the final evaluation. This dose reduction was statistically significant ($P = 0.001$). Cyclosporin was discontinued in three patients—in two because of unsatisfactory results and in one because of a disease flare-up after 9 months of successful treatment.

In the entire population, side-effects were experienced by 33 of 41 patients (80%) [27 of 34 (79%) systemic and six of seven (85%) uveitic cases], and led to the discontinuation of cyclosporin therapy in nine cases, all of whom were systemic patients not taking other second-line drugs (Table 2). The most frequent side-effect was an increase in serum creatinine to more than 30% above the baseline value (16 patients). In 13 cases this increase was dose-dependent and a 25% dose reduction was sufficient to restore normal values; in three cases the dose necessary to control the systemic signs or uveitis resulted in an unacceptable increase in creatinine and the therapy had to be abandoned (the discontinuation of therapy led to complete normalization). There were six cases (15%) of hypertension. The treatment needed to be terminated in three cases because of the persistence of high blood pressure after dose reduction. Treatment withdrawal led to complete normalization in two of these three cases; the third required the introduction of anti-hypertensive therapy. One child was withdrawn from treatment because of painful gastrointestinal disturbances with acute abdominal pain. Transaminases increased to more than twice the maximum reference values in three cases, leading to the discontinuation of treatment in one patient. One child discontinued treatment because of early and severe thrombocytopenia; prompt withdrawal of cyclosporin and treatment with a corticosteroid pulse and high-dose intravenous immunoglobulins resulted in the normalization of the platelet count.

TABLE 1. Reasons for drug discontinuation

	Systemic JCA (34 patients)	Uveitis (7 patients)
Disease remission	8 (23)	0
Disease flare-up	7 (20)	1 (14)
Inefficacy	8 (23)	2 (28)
Side-effects	9 (26)	0

Numbers in parentheses are percentages.

TABLE 2. Side-effects

	Whole study population (41 patients)	Systemic JCA (34 patients)	Uveitis (7 patients)
Hypercreatininaemia	16 (39)	13 (38)	3 (43)
Hypertension	6 (15)	6 (18)	0
Hypertrichosis	12 (29)	10 (29)	2 (28)
Gum hyperplasia	5 (12)	3 (9)	2 (28)
Intercurrent infections	3 (7)	3 (9)	0
Hypertransaminasaemia	3 (7)	3 (9)	0
Gastrointestinal disturbances	2 (5)	2 (6)	0
Thrombocytopenia	1 (2)	1 (3)	0
Pseudoacute abdomen	1 (2)	1 (3)	0
Gynaecomastia	1 (2)	1 (3)	0

Discussion

The efficacy of drug therapy in systemic JCA is particularly difficult to evaluate because of the variability of the course and outcome of the disease. The acute manifestations of systemic-onset disease may last from weeks to months and systemic features such as fever, rash and pericarditis may recur during the first few years. Roughly half of the children recover almost completely, whereas the others may develop progressive polyarthritis. The acute manifestations may respond to NSAIDs, but very high doses are frequently needed and may lead to toxic hepatitis or other adverse side-effects. Even when fever and joint swelling can be controlled by NSAIDs, severe anaemia with marked fatigue may become a major problem.

The chronic administration of corticosteroids to children should be avoided because it may delay growth in stature and increase the risk of secondary osteoporosis. The main objective of using DMARDs in systemic-onset JCA and chronic anterior uveitis due to pauciarticular-onset JCA is to control disease activity without corticosteroids or, in active corticosteroid-dependent cases, to obtain a corticosteroid-sparing effect. Various second-line drugs have been tried in an attempt to influence the progression of systemic-onset JCA [30], but it has been shown that gold salts and penicillamine have a high incidence of toxicity when administered during the systemic phase of the disease [31–34], azathioprine does not seem to lead to satisfactory long-lasting results and is potentially carcinogenic [35], and cyclophosphamide and chlorambucil, although

potentially effective, cannot be used for long periods because of their toxicity. High-dose intravenous immunoglobulins have not been found to be really effective in placebo-controlled trials [36], and cost and availability limit their use to selected situations. Methotrexate is the only drug shown to be well tolerated and useful in controlling systemic disease [37].

Our open prospective study (started in December 1987) was the first and remains the largest trial of cyclosporin in systemic JCA and uveitis due to pauciarticular-onset JCA. Previous reports on the efficacy of cyclosporin in JCA were positive [25, 27, 28], but these studies involved a more restricted number of systemic JCA patients (14, 7 and 10 in the three reports respectively) and had a shorter follow-up time. On the basis of the recommendations of previous studies, an average dose of 5 mg/kg per day was chosen in order to investigate whether the drug might have a disease-modifying and corticosteroid-sparing effect in corticosteroid-dependent patients and in those whose systemic disease or uveitic inflammation was unsatisfactorily controlled by conventional therapy.

The effects on arthritis did not turn out to be as positive as those on systemic symptoms. Five of the patients treated in an early phase of systemic disease were not arthritic. Moreover, following the administration of cyclosporin, all experienced the complete remission of systemic manifestations and did not develop arthritis, and concomitant drug therapy could then be withdrawn. However, after a period of remission lasting from 2 to 34 months, three of the patients relapsed with systemic symptoms and subsequently developed progressive polyarthritis. Additional treatment with cyclosporin once again resulted in fever control, but the drug was finally discontinued because of its inefficacy in arthritis.

The effects of cyclosporin on uveitic inflammation seem to be variable: the Tyndall score (usually considered an index of the intensity of uveitic inflammation) improved in the majority of the eyes involved (66%), but the average Tyndall score of the group as a whole was not significantly lower at the most recent evaluation than at baseline. Nevertheless, visual acuity improved in 58% of the eyes involved and the average visual acuity of the whole population improved significantly. This improvement was due to a reduction in the number of anterior chamber cells and/or anterior chamber flares, as well as to the successful surgical treatments (lensectomy and/or vitrectomy) that were performed in some patients. The ophthalmologist judged the results as positive in four patients: satisfactory in three patients in whom reductions in the Tyndall score and steroid dose were obtained, resulting in the feasibility of performing successful surgical treatment, and good in one patient, who obtained complete and persistent remission of ocular inflammation that has so far endured for 1.1 yr.

Some of the typical adverse effects of cyclosporin were observed in the majority of our patients, but they were of minor clinical relevance in most cases. Hypercreatininaemia and hypertension (the most frequent side-effects in our population) were usually dose-dependent and reversible upon dose reduction. The drug needed to be withdrawn because of the persistence of these side-effects, despite a dose reduction (in three patients because of hypercreatininaemia and in three because of hypertension). Although cyclosporin should not suppress the bone marrow, we would like to make particular reference to the case of a girl who, after 2 weeks of therapy at a dose of 5.2 mg/kg per day, and with blood cyclosporin levels within the therapeutic range, presented severe thrombocytopenia (her platelet count dropped from 700 000 to 6000/mm^3). Another unusual case that required withdrawal of treatment concerned an 8-yr-old girl with systemic-onset disease who, after 2 yr of therapy, developed painful gastro-intestinal disturbances with pseudoacute abdomen. The nature of this manifestation remains unknown, as the disease may present itself with peritonitis and/or adenomesenteric involvement in its systemic phases. Blood cyclosporin levels could not be assessed, but the discontinuation of the drug led to the prompt disappearance of the symptoms. An increase in liver enzymes is not frequent with cyclosporin treatment but, in one patient with systemic disease it was so immediate (1 week after introduction of cyclosporin) and so severe (serum transaminases increased to 100 times the baseline value) that it resulted in immediate drug withdrawal, which was followed by complete normalization.

One retrospective study [25] suggests that the most serious side-effect observed in children treated with cyclosporin for refractory JCA is the aggravation of anaemia. However, the decrease in Hb concentration in that study was unrelated to whole-blood cyclosporin levels and was dependent on the duration of treatment. In our study, Hb levels paralleled the course of the disease, increasing in patients whose condition improved and decreasing in those showing a poor response, particularly when the steroid dose had been tapered. The differences in the clinical results of these two studies may be attributed to the fact that all of the patients in the retrospective study had severe long-lasting disease, had been treated previously with several second-line drugs, including immunosuppressants, and were also receiving steroids, whereas our series involved 19 patients with early disease (of less than 24 months' duration), many of whom had never undergone treatment with second-line drugs. Our data are in accordance with other published studies indicating that cyclosporin does not interfere with erythropoiesis.

In the group of uveitic patients, the doses were slightly higher than in the systemic group (mean dose 4.4 and 3.4 mg/kg per day respectively) because of the risks connected with visual function, as uveitic patients were affected by long-lasting, severe, active, bilateral inflammation of the eyes, therefore at risk of blindness. These higher doses of cyclosporin were better tolerated by the uveitic patients, who showed a similar incidence of side-effects but in whom the effects were always mild, reversible and never led to withdrawal of therapy.

Blood levels of cyclosporin were measured frequently during the first years of our study, but we have decided more recently to limit determination to the beginning of therapy, in order to ensure that therapeutic levels are reached. We have found that a slow increase from an initial dose of 3 mg/kg per day to up to 5 mg/kg per day does not lead to an unpredictable rise in blood cyclosporin levels, and that monitoring blood pressure and serum creatinine is of greater value for the identification of side-effects.

In conclusion, our results suggest that cyclosporin may be used in some cases of systemic-onset JCA and chronic anterior uveitis associated with pauciarticular-onset JCA. However, only a minority of our patients achieved total disease remission and a quarter discontinued the drug because of side-effects. On the basis of our experience, recent-onset disease may respond to cyclosporin, possibly as a result of its inhibitory effects on cytokine production and T-cell recruitment and activation, and a corticosteroid-sparing effect may be obtained in some cases. Moreover, our results show that daily doses of up to 5 mg/kg per day are relatively safe in children. A controlled double-blind trial designed to establish unequivocally the therapeutic role of cyclosporin in JCA is therefore warranted.

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