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Cyclosporin treatment of nephrotic syndrome in adults: Results of the Société Néphrologie collaborative study

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SUMMARY

Although the pathophysiology of the idiopathic nephrotic syndrome (INS) has not been elucidated, there is evidence that, at least in minimal changes (MCD), it is provoked by an immunological disorder leading to secretion of lymphokines able to cationize both glomerular basement membranes and serum albumin.

The goal of this paper is to present the result of two studies using CsA (cyclosporin A) in the treatment of INS corticoresistant, corticodependent or in which steroid therapy is contraindicated, and MCD or focal and segmental glomerulosclerosis (FSGS) proven by recent biopsy.

In the first study, CsA was given alone at an initial dosage of 5 mg/kg/day, we analyzed the efficacy of therapy and the incidence of relapses atter CsA discontinuation. 56 patients were included, 32 corticoresistant, 19 corticodependent and 5 with contraindication to steroid therapy (23 with MCD and 33 with FSGS). 27 patients had been previously treated with conventional immunosuppresive drugs.

In the second study, still under way and with more stringent inclusion criteria, the response to CsA treatment (5 mg/kg/day, in form of soft gelatine capsules) in association with prednisone (maximum dose: 15 mg/day) was evaluated.

The combined results of Studies 1 and 2 (84 patients) are as follow: in corticodependent patient the remision rate was 74 % (22 patients) and in corticoresistant patients 26 % (14 patients). The sucess rate in MCD was of 80 % and in FSGS 20 %.

Side effects (such as GI diturbances, tremor, hypertrichosis, etc.) did not lead to CsA withdrawal. Renal function was unchanged in the whole group of patients studied. In the second study, the incidence of side effects was lower, in particular regarding gastrointestinal disturbances, which might be explained by the different presentation of CsA, in soft gelatin capsules.

Key words: ***Cyclosporin. Idiopathic nephrotic syndrome. Efficacy. Tolerance.***

TRATAMIENTO CON CICLOSPORINA DEL SÍNDROME NEFRÓTICO DEL ADULTO: RESULTADOS DEL ESTUDIO COOPERATIVO DE LA SOCIEDAD FRANCESA DE NEFROLOGÍA

Si bien no se ha determinado cuál es la fisiopatología del síndrome nefrótico idiopático (SNI), hay elementos que hacen suponer que, al menos en la nefropatía por cambios mínimos, es consecuencia de un trastorno inmunológico con secreción de linfoquinas que cationizan tanto la membrana basal glomerular como la albúmina sérica.

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Se exponen los resultados de dos estudios realizados empleando CsA (ciclosporina A) en el tratamiento del SNI corticorresistente, corticodependiente o con contraindicación al tratamiento esteroideo, con lesión (cambios mínimos, glomeruloesclerosis focal o segmentaria) comprobada mediante biopsia renal reciente.

En el primer estudio se administró CsA sola a la dosis inicial de 5 mg/kg/día, valorándose la eficacia del tratamiento y la incidencia de recaída tras su supresión. De los 56 pacientes incluídos, 32 eran corticorresistentes, 19 corticodependientes y cinco con contraindicación al tratamiento esteroideo (23 con nefropatía por cambios mínimos y 33 con glomeruloesclerosis focal y segmentaria). Veintisiete pacientes habían sido tratados previamente con fármacos inmunosupresores convencionales.

En el segundo estudio, todavía en curso y con criterios de inclusión más restrictivos, se valoró la respuesta al tratamiento asociando prednisona (dosis máxima de 15 mg/día) a la CsA (5 mg/kg/día), administrada ésta en forma de cápsulas de gelatina blanda.

Los resultados combinados de los dos estudios (84 pacientes) son los siguientes: en los pacientes corticodependientes la tasa de remisión es del 74 % (22 pacientes) y en los corticorresistentes del 26 % (14 pacientes). La tasa de éxito en la nefropatía por cambios mínimos es del orden del 80 %, mientras que en la glomeruloesclerosis focal y segmentaria es del 20 %.

La aparición de efectos secundarios (tales como transtornos gastrointestinales, temblor, hipertricosis, etc.) no obligó a interrumpir el tratamiento. En ningún paciente del grupo estudiado la función renal resultó alterada. En el segundo estudio, la incidencia de efectos secundarios fue inferior, especialmente a nivel gastrointestinal, debido probablemente a la administración de ciclosporina en forma de cápsulas de gelatina blanda.

Palabras clave: ***Ciclosporina. Síndrome nefrótico idiopático. Eficacia. Tolerancia.***

Introducción

Idiopathic nephrotic syndrome (NS) due to minimal changes (MCD) or lesions of focal and segmental glomerulosclerosis (FSGS) represents approximately 30 % of all adult cases of NS[1]. Response to corticosteroid theraphy is much favorable in MCD than it is FSGS. However, corticoresistance or corticodependency or a multirelapsing course leads to long-term corticosteroid toxicity. When alkylating agents have not obtained stable remision, the disease follows a chronic course maked by numerous complications.

The pathophysiology of idiopathic NS has not been elucidated. However, there are arguments to believe that, at east in CMD, it is provoked by an immunological disorder leading to secretion of lymphokines able to cationize both glomerular basement membranes and serum albumin[3-6].

On these considerations, some investigators, including ourselves, undertook in 1984-85 pilot trials on the treatment with cyclosporine A* (CsA) of corticoresistant or corticodependent idiopathic NS. These trials should be mostly considered as «feasibility» studies. However, they demonstrated that in some cases where NS had resisted all sorts of conventional regimens, CsA obtained remission with encouraging renal and extrarenal tolerance.

The interpretation of most of the preliminary studies was difficult because of the diversity of protocols used. This is why the Société de Néphrologie undertook a collaborative study in 1986 to assess the efficacy and tolerance of CsA in adult idiopathic NS, with a protocol in which CsA was used alone for 3 months. In the mean time, the Sociedad Española de Nefrología launched a large-scale study, the conclusions of which appeared in 1988[6] and were ramarkably confirmatory of the Société de Néphrologie ongoing experience. In 1988, a second protocol was designed by the Société de Néphrologie, in which CsA was associated with low-dose prednisone, to determine whether such an association increased the efficacy of the immunosuppresive regimen. This second protocol is still under way.

The goal of this paper is to present the data obtained from Protocol 1, and to give an interim report on Protocol 2 as of February 1990.

Patients and study design

Study 1

Patients were enrolled on the basis of idiopathic NS; corticoresistance or corticodependency or contraindication to corticosteroid treatment; and MCD or FSGS proven by recent renal biopsy. Patients with BP > 180/100 mmHg, creatinine clearance < ml/min, liver disease, pregnancy or infection were excluded.

* Sandimmun®

Table I. Total + partial remission and failure in patients enrolled in Studies 1 and 2 according to their previous response to corticosteroid therapy

Study 1 (n = 51)		Study 2 (n = 33)	
Results of each study according to corticosensitivity:			
Remission	**Failure**	**Remission**	**Failure**
CD (n = 19)		CD (n = 11)	
14	5	8	3
CR (n = 32)		CR (n = 22)	
9	23	5	17
Overall results per study:			
Remission	**Failure**	**Remission**	**Failure**
23	28	13	20

Update Feb. 1990.
(CD = corticodependent, CR = corticoresitant.)

After an 18-day placebo period, CsA alone was started at an initial dosage of 5 mg/kg/day (in two divided does, 12 hours apart), subsequently tirated for target whole blood tough level of 200-800 ng/ml (12-hour post-dose, RIA, polyclonal ab). The main goals of the study were to assess the efficacy of CsA treatment at 3 months and the incidency. In cases after discontinuation, i.e., CsA dependency. In cases where relapse occurred, investigators were free to resume CsA, alone or with additional corticosteroids.

Study 2

We enrolled patients basically on the same creterias as in Study 1. The differences stemmed from: a) more stringent inclusion criteria as regards renal function, b) more rigid monitoring of renal toxicity: patients were withdrawn from the study if serum creatinine rose by 30 % over baseline and remained elevated despite two successive reductions in CsA dosage, and c) more accurate definition of «complete remission», «partial remision» and «failure». Results were assessed as: complete remission = proteinuria <0.5 g/24 hours and serum albumin > 3 g/dl, partial remission = proteinuria between 0.51 and 3.0 g/24 hours and serum albumin >3 g/dl, and failure as proteinuria >3 g/24 hours, irespective of serum albumin levels. Thus, patients with clear-cut improvement in clinical status, serum albumin rise over 3 g/dl (including cases where it returned to normal), but where 24 h proteinuria remained in excess of 3 g were considered «failures» whereas in Study 1 they were accepted as «partial remission».

Study 2 included the association of low-dose prednisone with CsA. Sandimmun was supplied in a new presentation in which the oily solution was encapsulated in soft gelatine capsules. The study design varied according to previous response to corticosteroids. Prednisone was tapered to 0.2 mg/kg/day in the corticoresistant group, with a maximun of 15 mg/day. CsA was begun at a dose of 5 mg/kg/day and subsequently adapte for target whole blood trough levels 12 hours post-dose of 100-200 ng/ml (specific monoclonal ab). Full-dose CsA treatment was given for 6 months, and for 9 months for those in partial or complete remission at months 6, followed by slow tapering to a stop at 12 months, aimed at determining the «cyclosporine dependency» of responsive patients.

Results

1. EFFICACY

Study 1

56 patients, aged 31.8 ± 14 years (range 14-69) were enrolled, including 32 corticoresistant, 19 cortitcodependent and 5 with a ontraindication to corticosteroid treatment. NS had evolved 54 ±63 months before the trial. 27 patients had at some time been treated with conventional immunosuppressivedrugs. 23 patients were classified as having MCD and 33 as FSG. In the MCD group, 15 were cortidependent and 8 corticoresistant; in the FSG group, 6 were corticodependent and 27 were corticoresistant. Before treatment, systolic BP was 126.4 ± 15.7 mmHg, diastolic BP was 78.4 ± 10.4, serum creatine was 104± 45 µmol/l and creatinine clearence was 92 ±35 ml/min. The results are summarized in Tables I, II, and III.

Results at 3 months

Five patients did not complete the 3-month protocol (due to side effects in 4 and to nonrelevant death in one). In the 51 remaining cases, the success rate in MCD was significantly higher than in FSGS, with complete + patial remission in 15/23 patients in the former versus only

Table II. Combined results of Studies 1 and 2 according to previous corticosensity of enrolled patients

	Remission	Failure
Corticodependent patients (Total 30)	22 (74 %)	8 (26 %)
Corticoresistant patients (Total 54)	14 (26 %)	30 (74 %)

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Table III. Combined results of Studies 1 and 2 according to histology at inclusion

		Complete remission	Partial remission	Failure
Study 1 (51 pts)	MCD (23)	13 (56 %)	2 (9 %)	8 (35 %)
	FSG (28)	5 (18 %)	3 (11 %)	20 (71 %)
Study 2 (33 pts)	MCD (19)	8 (42 %)	1 (5 %)	10 (53 %)
	FSG (14)	2 (14 %)	2 (14 %)	10 (72 %)

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8/28 in the latter. Response to CsA also varied according to previous responsiveness to corticosteroids, with complete + partial remission observed in 14/19 corticosteroid-dependent patients versus 9/32 corticoresistant patients.

Results at 6 months

Results at 6 months, analyzed in 24 patients (13 MCD and 11 FSGS) showed 13 successes in the MCD group, compared to 6 in the FSGS group.

Results at 12 months and beyond

Nineteen patiens were treated with CsA for at least one year. Remission maintained in 17 cases, with CsA alone in 8 and with an association of low-dose corticosteroid therapy in 9. Renal function was better than at the beginning of treatment in 8 patients, stable in one, slightly impaired in 8 and impaired in 2 (one case of MCD and one of FSGS).

Study 2 (Update Feb. 1990)

A total of 33 patients, aged 35.5 ±15 years (range 19-66) have so far been enrolled, including 22 corticoresistant and 11 corticodependent. NS had evolved 40 ± 68.2 months before the trial.

Results at 3 months

Results so far obtained seem to indicate that the efficacy of combined CsA plus low-dose prednisone is not different from the results recorded in Study 1, with the same clear difference in the response rate between corticodependent and corticoresistant patients, whatever renal histology. Of corticodependent patients, complete remission was achieved after a period which varied from 1 week to 9 months. Patients in whom complete remission was obtained after more than 3 months went progressively through phases of «failure» followed by «partial remission» which eventually led to «complete remission». Attempts to taper CsA dosage were almost invariably followed by relapse of proteinuria. Most successful cases were CsA dependent and there was a threshold dose under which disease activity escaped treatment.

Results at 6 months

Continuing treatment over a second trimester led to an increased number of partial or complete remissions.

Results at 12 months and beyond

Are not yet fully interpretable, due to the limited number of cases.

2. TOLERANCE

Study 1

Minor side effects (such as GI disturbances, tremor, hypertrichosis, etc.) were frequent, but did not lead to withdrawal. Renal function was unchanged in the whole group of patients studied. Systolic blood pressure was slightly elevated in the whole group and a trend toward elevated systolic and diastolic blood pressure was noted in the 28 cases with treatment failure, most of which were FSGS. Is was also in FSGS that major side effects led to withdrawals. Repeat renal biopsy was perfomed in 16 cases, of whom 10 were MCD. In 3 of them, lesions of FSGS were visible on the repeat biopsy. Of the 16, definite images of CsA toxicity were present on 2 repeat samples, 1 an MCD patient with stable serum creatinine at 100 ml/l, and the other a case of FSGS who had received protracted treatment despite absence of remission.

In 3 patients, malignancy was discovered after a year of treatment with CsA. The first was a case of Hodgkin's disease which was considered by the investigators more likely to be the causa of nephrosis that the consequence of CsA treatment. Two patients aged over 60 developed respectively squamous cell cancer of the lung and epithelioma of the endocervix.

Study 2

Minor side effects recorded were much less than in Study 1. This, in particular regarding gastrointestinal disturbances, might be explained by a different presentation of CsA, in soft gelatine capsules. Major side effects, including rapidly rising serum creatinine levels or hypertension, led to discontinuation of treatment before 3 months in only two cases (both with FSGS) and at 3 to 4 months in 2 cases (both with FSGS). Two patients defaulted at 3

months and in a third the investigator stopped treatment due to lack of efficacy. In the other cases treatment was stopped at 6 months due to failure as specified in the protocol, and not to side effects.

Comments

The experience of the Société de Néphrologie is now based on 84 cases. Renal tolerance has not only been assessed by meticulous monitoring of renal function throughout the study but also in 25 cases by repeat renal biopsy. This tolerance was superior in adults to that in children, as judged on compatison of our experience with that of Niaudet et al.[4,7]. Whether such lesser renal toxicity in the adult is attributable to lesser dosage or to some other factor pertaining to the backgroup remain to be elucidated. At any rate, the risk of interstitial and/or vascular lesions appears distinctly greater in patients with initial lesions of FSGS than in those with MCD.

Study 2 was designed to determine whether a low dose of prednisone added efficacy to CsA treatment in corticosteroid restant cases. Such an improvement in efficacy with CsA + prednisone versus CsA alone has been demonstrated[7]in children. In this respect, the results of Protocol 2 were disapointing, as the percentage of «successes» versus «failures» was comparable to Study 1. This can be interpreted in two ways. The first is that, for some reason relevant to pathophysiology, response of children to treatment is not comparable to that of adults. The second, which we are inclined to favor, is that prednisone dosage was insufficient and that we might have increased efficacy, either with doses or with intermittent monthly pulses of methylprednisolone. This calls for further trials.

At any rate, the experience acquired by the so-far largest series of adult patients treated with CsA for idiopathic syndrome allows the definition of guidelines for use of CsA in this indication. Our recommendations are therefore.

1. Select patients reasonably

The best indications is corticodependent MCD, where the success rate is in the order of 80 % and the risk of long-term renal toxicity averages 10 %. Conversely, a patient with corticoresistant FSGS has a 20 % chance of success. In addition, when in a patient with FSGS pre-CsA serum creatinine is already over 150 µmol/l, when hypertension is present and when tubulointerstitial lesion are already visible on the pretreatment biopsy, the risk of deteriorating renal function is in the order of 85 %, including both increased tubular and vascular toxicity of CsA and the natural development of the glomerular focal and segmental lesions. Such patients should probably be excluder or at least inclusions should be very carefully weighed. In addition, embarking on CsA treatment in a nephrotic patient of more than 60 years of age should be envisaged reluctantly, as in this age group the risk of overlooked underlying tumour is certainly greater, and cancer could conceivably be ascribed by the patient or his family to CsA treatment.

2. Monitor treatment meticulously

The initial dosage should be no more than 5 mg/kg/day. Dosage should be monitored each week until stable trough levels have been attained. The 12-hour postdose trough levels should be aimed at no more than 200 ng/ml whole blood (monoclonal antibody). Dosage should be decreased immediately when serum creatinine rises by more than 30 % over baseline and persistent reduction of the GFR should lead to discontinuation of treatment. Finally, knowing that the histological lesions of CsA toxicity may precede the decline in renal function, decision to continue treatment after one year in a «cyclosporine-dependent» patient should only be taken after verifying that the renal interstitium and renal vessels are still unharmed on repeat renal biopsy.

3. Accept failure modestly

Most cases of renal toxicity that were observed in Study 1 appeared in patients with FSGS, in whom frank remission had not been obtained within 6 months and investigators obstinately continued treatment in the hope of delayed remission. Thus, 6 months seems a reasonable legth of treatment to decide withdrawal or continuation.

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