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Chronic Interstitial Lung Disease in Children: Response to High-Dose Intravenous Methylprednisolone Pulses

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Summary. The prognosis for children with chronic interstitial lung disease is poor and the mortality rate is high, especially in infants. This explains the many therapeutical protocols which have been proposed and investigated by several authors. In the present work, we evaluated the response of three infants with idiopathic pulmonary fibrosis to high-dose intravenous prednisolone pulses. The patients were referred to the department at the age of 4, 17, and 3 months, respectively. The diagnosis was confirmed by open lung biopsy and intravenous pulse methyl prednisolone therapy was started with the following protocol: 300 mg/m^2 methylprednisolone daily for 3 days, repeated every 4 to 6 weeks. Because of the extreme severity of the respiratory distress at the time of diagnosis, the intravenous pulse treatments were initially complemented by oral prednisone. Clinical improvement was noticed within 6 months with progressive correction of hypoxemia. After follow-up for 3.5 to 4 years, with a total number of pulses of 37, 26, and 32, respectively, the children are symptom-free and do not require oxygen supplementation. During this period, no side effects and no adrenal insufficiency could be documented. Based on current knowledge of steroid action, it can be speculated that the response to intermittent high-dose intravenous methylprednisolone may explain the ability of this mode of hormone administration to maintain an adequate level of glucocorticoid receptor expression. More information and trials through multicenter collaborations are needed to assess therapeutical protocols of repeated high-dose intravenous steroid treatment. **Pediatr Pulmonol. 1998; 26:332–338.**

Key words: pulmonary fibrosis; children; methyl prednisolone; pulse therapy; interstitial lung disease.

INTRODUCTION

Chronic interstitial lung diseases include a large variety of disorders which can be classified as diseases of known and of unknown etiology.[1–8] If the onset of the disease is largely dependent on factors that initiate the process, progression is associated with the development of an inflammatory response. In recent years much has been learned about the mechanisms involved in this response, and it is now established that they share a number of similarities in the various pathological situations.[9–12]

The major aim of various therapeutic strategies in chronic interstitial lung diseases is to decrease and suppress inflammation in order to reverse the deleterious processes and restore normal structure and function. To achieve this goal, several treatments have been proposed which include glucocorticosteroids as well as other pharmacological agents such as chloroquine, cyclophosphamide, and azathioprine.[1,13–16] In the few reports in the literature, the beneficial effects of drugs other than steroids are difficult to evaluate, due to the small number of patients treated, the heterogeneity of the diseases included, and differences in the therapeutic protocols.[17]

Therefore, at the present time corticosteroids represent the major anti-inflammatory agents for the treatment of chronic interstitial lung diseases. In most cases, the therapeutic strategy used has been oral prednisone, and it is generally accepted that the response to steroid therapy is one of the most important factors determining prognosis. Failure to respond to oral prednisone has been reported in several studies. This suggests that various protocols of steroid administration are currently being used. Among them is the use of high-dose intravenous methylprednisolone pulses. Recently, we reported our experience with ten infants with idiopathic pulmonary fibrosis.[18] In all

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cases the diagnosis was made before the end of the first year of life and was confirmed by open lung biopsy. Nine infants were treated with oral prednisone alone or in combination with other immunosuppressive agents and all nine died. One additional infant was treated with pulses of methylprednisolone because of failure to respond to oral prednisolone. This patient displayed similar clinical, radiological, and histological abnormalities as the other children at the time of diagnosis and was the only one who survived. Based on this observation, we decided to use high-dose intravenous methylprednisolone pulses in the management of children with chronic interstitial lung diseases. We report here the response of three children who were referred to the department for treatment of idiopathic pulmonary fibrosis and who received high-dose intravenous methylprednisolone therapy.

MATERIALS AND METHODS

Patients

Three small children (two girls and one boy) were included in this prospective study. They were referred to the pediatric pulmonary department at the age of 4, 17, and 3 months because of respiratory distress and cyanosis. Histories were reviewed for duration and severity of symptoms, as well as family history. Initial pulmonary evaluation included physical examination, chest roentgenography, arterialized capillary blood gas determinations during air breathing, and bronchoscopy with bronchoalveolar lavage (BAL).[19] Among the other investigations were blood cell counts and routine biochemical tests, complete immunological studies, sweat chloride concentrations, microbiological studies, cardiac evaluation (electrocardiogram and echocardiogram), and a barium swallow. Once the diagnosis was established based on the result of open lung biopsy, patients were regularly assessed for clinical, radiological, and pulmonary function improvement. Pulmonary function tests included blood gas determinations, measurements of functional residual capacity (FRC), dynamic lung compliance (CL,dyn), total pulmonary resistance, and lung transfer for CO ($T_{L,CO}$).[20] Results of these tests were expressed as a percentage of the predicted values for height-matched children.

Abbreviations

AP-1	Activator protein 1
BAL	Bronchoalveolar lavage
CL,dyn	Dynamic lung compliance
FRC	Functional residual capacity
NF-kB	Nuclear factor kB
PAS	Periodic Acid Schiff
$T_{L,CO}$	Lung transfer coefficient for CO

Tolerance of glucocorticoid treatment was assessed by evaluating the effects on the hypothalamic-pituitary-adrenal axis, using measurements of plasma ACTH concentration, morning plasma cortisol level, and adrenal reserve by the short tetracosactrin test.[21] Plasma ACTH and cortisol levels were measured before tetracosactrin stimulation (time 0) and again 30 min after tetracosactrin stimulation. Response to glucocorticoid treatment also included evaluation of effects on growth (height) and bone metabolism (measurements of serum and urinary calcium and phosphate, serum-alkaline phosphatase), as well as cataract formation and metabolic effects (mainly glucose metabolism).

Bronchoscopy and BAL

Bronchoscopy and BAL were performed as previously described.[22] Briefly, bronchoscopy and BAL were done under local anesthesia. The bronchoscope was introduced into a lower right lobe segment. The volume of normal saline (0.15 N NaCl) used was equivalent to 10% of the predicted FRC. The sterile solution was injected in six aliquots. Only the last five aliquots of aspirated fluid were collected. One sample of the recovered BAL fluid was used for microbiological studies. Cytological studies included total and differential cell counts after cytocentrifuge preparation.

Histological Analysis of Lung Biopsy

Open lung biopsy was performed under general anesthesia and analyzed as previously described.[1,18] Part of the specimen was fixed in glutaraldehyde 2.5% for electron microscopy processing and another part was deep frozen. Specimens for histology were formalin- or Bouin-fixed, paraffin-embedded, and stained with hematoxylin and eosin Masson blue trichrome, PAS, Perls, Giemsa, reticuline, and methenamine silver stains. The histological changes were graded according to the extent of alveolar wall thickening, severity of interstitial fibrosis, interstitial infiltration with inflammatory cells, and degree of cellular accumulation in the alveolar spaces.[1,18]

RESULTS

Presentation of the Patients and Diagnosis

Characteristics of the patients when referred to the pulmonary department are given in Table 1. Onset of symptoms, mainly cough and tachypnea, occurred approximately 2 months before diagnosis. In Patient 3, a Respiratory Syncytial virus infection was associated with a rapid deterioration of the respiratory status. The patients were referred to the department at the age of 4, 17, and 3 months. Clinical presentation at initial evaluation

TABLE 1—Characteristics of Patients at Initial Evaluation

	Patient 1	Patient 2	Patient 3
Age at diagnostic (months)	4	17	3
Age at onset of disease (months)	2	15	1
Cough	Present	Present	Present
Tachypnea	Present	Present	Present
Inadequate weight gain	Present	Present	Present
Chest radiograph			
Interstitial infiltrates	Present	Present	Present
Alveolar infiltrates	Absent	Present	Present
P_aO_2 (mmHg)	28	62	44
P_aCO_2 (mmHg)	42	37	40
BAL fluid			
Total cell counts $\times 10^3$/mL	1,500	1,900	200
Macrophages (%)	76	89	73
Lymphocytes (%)	6	6	8
Neutrophils (%)	13	5	18

BAL, bronchoalveolar lavage.

and results of arterialized capillary blood gases are given in Table 1. Chest radiographs showed abnormalities in all patients. In two cases, mixed interstitial and alveolar infiltrates were observed. In the other child, mainly interstitial infiltrates were described. The bilateral abnormalities were confirmed by CT scan.

Bronchoscopy and BAL were performed in the three patients and BAL total and differential cell counts are listed in Table 1. The results were compared to published normal values[23] which indicated: (mean ±SD): total cell number: $350.6 \pm 178.1 \times 10^3$ cells/mL; percent macrophage population: 89.9 ± 5.3%; percent lymphocyte population: 8.9 ± 5.4%; percent neutrophil population: 1.2 ± 1.1%. Results indicated that total cell counts were dramatically elevated in two patients, with an increase in the percent of neutrophils in all children.

Open lung biopsy was performed within 3 weeks after admission. The findings (Table 2) were similar to the results described previously in the group of 10 infants with idiopathic pulmonary fibrosis. Intense to moderate fibrosis was present in all cases. Thickening of alveolar wall was due to expansion of cellular matrix, with large numbers of proliferating fibroblasts and dense deposits of collagen and elastin fibers. Cells infiltrating the alveolar septa were mainly fibroblasts and monocytes. Polymorphonuclear cells were observed in small amounts. Type 2 pneumocyte hyperplasia, a characteristic finding in pulmonary fibrosis, was always present. Alveolar content was dominated by macrophages. No bronchiolar obstruction was encountered. There was no histologic evidence of malformations or aspiration.

Treatment and Outcome

On diagnosis, intravenous pulse methyl prednisolone therapy was immediately started using 300 mg/m^2 methylprednisolone daily for 3 days, repeated once every 4 to 6 weeks. Because of the extreme severity of the respiratory distress at the time of diagnosis, the intravenous treatment was supplemented with oral prednisone, initially 2 mg/kg/day, rapidly followed by gradual tapering guided by the disease status and aiming at the lowest dose of oral prednisone possible and gradual conversion to alternate-day therapy. The total duration of oral corticosteroids was 6 months for Patient 1, 12 months for Patient 2, and 6 months for Patient 3. Therapy also included supplemental oxygen, adjusted to produce acceptable oxygen saturation and adequate nutritional support.

Clinical improvement was noticed within 6 months in all three patients. At the present time, after follow-up for 4 years in Patient 1, 3 years in Patient 2, and 3.5 years in Patient 3, they are symptom-free. Decreases in chest radiographs and CT scan abnormalities are also observed. Progressive improvement of arterial blood gases and pulmonary function tests was documented, as illustrated in Figure 1. Hypoxemia progressively lessened, and oxygen supplementation could be stopped after 18 months in Patients 1 and 3 and after 12 months in Patient 2. Results of pulmonary function tests indicated normalization of $T_{L,CO}$ in Patients 2 and 3. Improvement of CL,dyn in these two patients was also noticed, but the values remained below the normal range. By contrast, no significant changes in either $T_{L,CO}$ and CL,dyn were noted in Patient 1. After the first year of pulse therapy, BAL data indicated that total cell counts were within the normal range for all three patients; the percent of neutrophils was 2%, 5%, and 1%, respectively. Weight curves also displayed progressive improvement: from the 10th to the 25th percentile for Patient 1; from the 25th to the 90th percentile for Patient 2, and from the 3rd to the 50th percentile for Patient 3. Similar changes in height–growth curves were observed: from the 25th to the 50th

TABLE 2—Analysis of Lung Biopsy Material

		Alveolar septa						Alveolar lumen		
Patient	Alveolar wall thickening	Edema	Fibrosis	Elastin fibers	L	M/F	PN	L	M	PN
1	+++	++	+++	+++	+	+++	+	+	+++	–
2	+++	++	+++	++	+	+++	+	++	+++	–
3	+++	++	++	++	+	++	+	++	++	+

L, lymphocytes; M, monocytes and macrophages; F, fibroblasts; PN, polymorphonuclear cells.

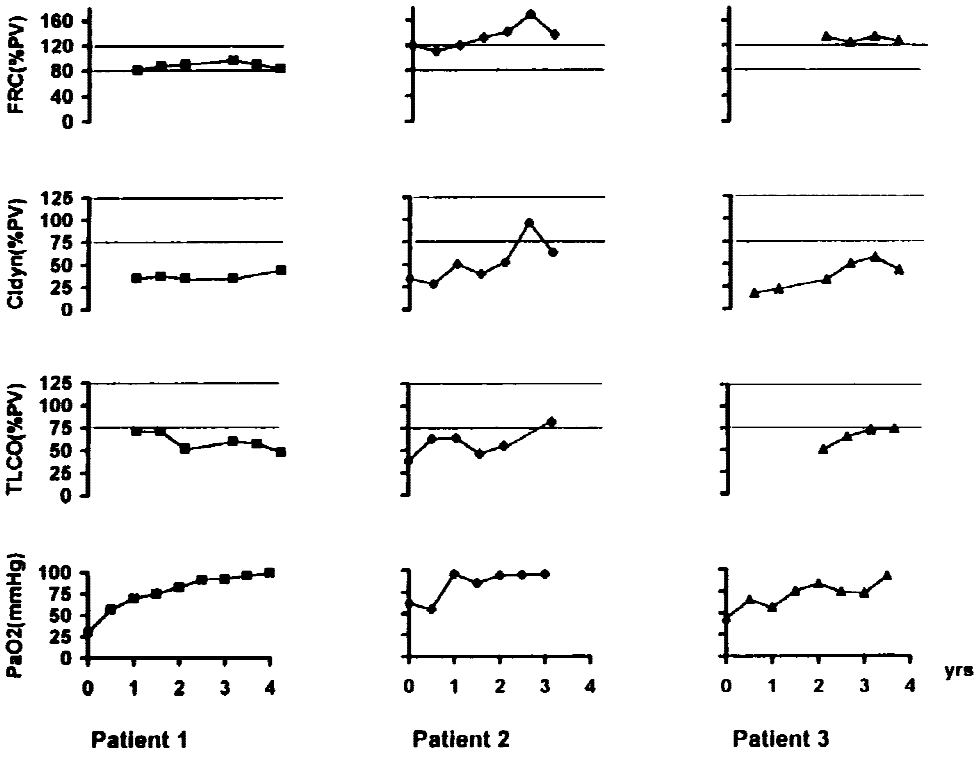

Fig. 1. Results of pulmonary function tests during follow-up of three patients with interstitial lung disease and treated with intermittent i.v. methylprednisolone pulses. Results of FRC, CL,dyn, $T_{L,CO}$ were expressed as a percentage of predicted values (%PV) for height-matched children. Horizontal lines indicate the range of normal values.

percentile for Patient 1; from the 25th to the 50th percentile for Patient 2, and from the 3rd to the 50th percentile for Patient 3.

At the present time the three children receive pulse corticosteroid therapy every 2 months. So far, the total number of 3-day courses of intravenous pulse methylprednisolone therapy has been 37 in Patient 1, 26 in Patient 2, and 32 in Patient 3. The children are monitored routinely for side effects. No cushingoid changes have been observed during follow-up. Blood pressure, fasting serum glucose levels, and urinalysis results remained normal. No osteoporosis, cataracts, or opportunistic infections have been noticed. Evaluation of the hypothalamic–pituitary–adrenal axis was repeated during follow-up; results are listed in Table 3. No abnormalities could be found in the tests performed on Patient 1. In Patient 2, a transient adrenal insufficiency was observed during the first year of treatment. In Patient 3, the results have been within the normal range.

TABLE 3—Evaluation of Hypothalamic–Pituitary Axis by Tetracosactrin Test

Patient	Follow-up (years)	Plasma ACTH (pg/mL)	Morning plasma cortisol (ng/mL)	Cortisol after tetracosactrin test (ng/mL)
1	0.5	—	—	—
	1	—	—	—
	2	28	178	271
	3	44	120	147
	4	21	119	250
2	0.5	12	<5	6
	1	9	<7	8
	2	69	58	209
	3	70	62	212
3	0.5	32	59	357
	1	22	83	541
	2	20	57	375
	3	27	91	272

DISCUSSION

The prognosis for children with chronic interstitial lung disease is poor, specially in infants, and there continues to be a high mortality rate.[17,18,24] This explains the various therapeutical protocols which have been proposed and investigated by several authors.[1,13,14,17] In the present work, we report the response of three infants with idiopathic pulmonary fibrosis to high-dose intravenous prednisolone pulses. The three infants responded to the corticosteroid pulse treatments differently. Patient 1 improved clinically shortly after starting the treatment, with progressive correction of hypoxemia. However, during the follow-up period no significant changes in the pulmonary function tests could be observed. For Patients 2 and 3, the beneficial effect of the treatment was associated with normalization of $T_{L,CO}$ and improvement of CL,dyn. These results share similarities with the response to methylprednisolone treatment reported by Kerem et al.[25] in a 4-month-old boy with chronic interstitial pneumonitis confirmed by open lung biopsy. On diagnosis, this infant received a three-day course of intravenous corticosteroid therapy at a dose of 15 mg/kg/

day. The pulses were repeated monthly seven times and were associated with a rapid clinical and functional improvement. The follow-up indicated that 4 months after discontinuation of therapy, the patient remained symptom-free and thriving.

It is important to point out that no side effects could be documented during the follow-up period in the present study. Evaluation of the hypothalamic–pituitary–adrenal axis revealed a transient adrenal insufficiency in only one child. It may be important that this insufficiency was observed in the patient who received oral prednisone for the longest duration. The good tolerance of high-dose methylprednisolone is in agreement with Kerem et al.[25] and their patient did not display any obvious side effects. However, in their report they did not give information on adrenal function.

The use of intravenous pulses of steroids has been reported in the treatment of various diseases. Wallaert et al.[26] evaluated the effects of high-dose methylprednisolone pulse therapy in sarcoidosis and noticed immediate improvement of all patients. The efficacy of such therapeutic was also evaluated in active lupus nephritis by Bertoni et al.[27] A significant improvement in multiple objective indices of disease activity was observed following high doses of intravenous corticosteroids, even in patients with recent worsening of renal function. Similar beneficial effects were reported by Galli et al.[28] in children suffering from severe atopic dermatitis who were unresponsive to standard therapy. After administration of a methylprednisolone bolus, an improvement of skin lesions and itching was noticed for several months.

These observations raise questions about the mechanisms by which high-dose pulse corticosteroid treatment may be more effective than continuous prednisone therapy at lower doses.[29] Answers to these questions remain hypothetical. It has been suggested that pulse treatment may induce stronger immunosuppressive effects with lower long-term toxicity. In the past few years, much has been learned about the cellular and molecular mechanisms of steroid action.[30] The biological effects of glucocorticoids are mediated by intracellular glucocorticoid receptors which, when bound to homologous ligand, function as DNA-binding proteins that enhance or repress transcription of responsive genes.[31] Also, glucocorticoid receptors can interact directly with other transcriptions factors such as AP-1 and NF-kB.[32,33] These direct protein–protein interactions, which could occur within the nucleus or within the cytoplasm, represent important elements in the control of inflammatory responses.

It is now well established that the ability of glucocorticoids to act on a specific tissue and to elicit their biological effect requires the presence of intact receptor molecules.[34] In addition, a direct correlation between the concentration of glucocorticoid receptor in a cell and its sensitivity to glucocorticoids has been documented in various cell systems.[35–37] Therefore, the number of active receptors is considered the key factor controlling the response to glucocorticoids.[34] The mechanisms involved in glucocorticoid receptor regulation are complex and include changes in receptor degradation and synthesis, as well as receptor inactivation (nonbinding forms).[34,38] From studies performed in cell cultures and on animals and humans, it is recognized that glucocorticoid receptors undergo downregulation after exposure to ligand.[37] In an interesting series of experiments on rat brain, McEwen et al.[39] showed that similar reductions in the number of glucocorticoid receptors were found in animals after stress-induced secretion of cortisol and following glucocorticoid treatment in unstressed rats. All these studies indicate that the reduction in receptor number may be an adaptative process and represent a common negative feedback mechanism protecting cells from the continued signals induced by glucocorticoid molecules.[36,37,40,41] Based on research data as well as clinical observations, it can therefore be suggested that chronic glucocorticoid treatment may lead to a desensitization of cells and of patients to subsequent hormone administration. A number of recent studies support this hypothesis.[41] As an example, Knutsson et al.[40] showed that intranasal glucocorticoid treatment in healthy subjects was associated with a significant decrease in glucocorticoid receptor mRNA levels in peripheral lymphocytes and in nasal mucosa.

These observations may help in the discussion of the results reported herein. From the observations that therapeutic steroid pulses were associated with a significant clinical and functional improvement of the patients, it can be assumed that this mode of treatment contributed to maintain an adequate number of functional glucocorticoid receptors. Intermittent administration of high doses of methylprednisolone may be effective by preventing the downregulation and/or promoting the positive regulation of glucocorticoid receptors.[34] The observations reported by several groups of patients' failure to respond to daily oral prednisone given at maximal dose may be explained by an opposite, inhibitory effect of such treatment on glucocorticoid receptor expression. In view of these findings, the initial addition of oral steroids to pulse therapy may not have been indicated in the present study. The reason for adding prednisone was empirical. It seemed justified because of the extremely critical clinical presentation of the patients on admission and on the lack of references in the literature on the efficacy of intermittent corticosteroid treatment in such pathological situations. Although the protocol we followed was to rapidly decrease the amount of oral prednisone, a better strategy might have been to discontinue oral prednisone shortly after the start of methylprednisolone.

In order to define the best steroid therapeutic regimen, several questions need to be addressed:

1) the frequency at which the intravenous administration should be performed;
2) the benefit of adding oral prednisone and the doses required; and
3) the duration of methylprednisolone therapy with identification of criteria for discontinuing the treatment.

In the present report, the beneficial effects were documented mainly by clinical and blood gas results. Based on the persistence of lung function abnormalities, we chose not to stop the treatment, but to progressively increase the intervals of pulse administration. However, this strategy is not based on long-term follow-up or placebo-controlled trials. Clearly, biological criteria evaluating the degree of lung inflammatory processes are needed to determine whether to continue or end pulse steroid therapy.

We conclude that high-dose intravenous methylprednisolone pulses seem to be an effective treatment for chronic interstitial lung disease in children. More information and evaluations through multicenter trials are now needed to evaluate this form of corticosteroid therapy.

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