CLINICAL RESEARCH

Remission of idiopathic nephrotic syndrome after treatment with cyclosporin A

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Abstract

Nephrotic syndrome in minimal change lipoid nephrosis and focal segmental glomerulosclerosis may be due to alteration of glomerular anionic sites by a lymphokine. Six adults with nephrotic syndrome who were resistant to treatment with corticosteroids and immunosuppressants were treated with cyclosporin A. In three patients with minimal change lipoid nephrosis who had been nephrotic for 3.5 to 23 years proteinuria resolved within 12 to 42 days. Subsequently, these patients became dependent on cyclosporin A. In three patients with focal segmental glomerulosclerosis who had been nephrotic for four to six years mean (SD) 24 hour urinary protein decreased from 14.7 (8.4) g to 3.6 (0.6) g within 20 to 25 days, serum albumin concentration rose, and oedema subsided. One patient died of myocardial infarction when still in partial remission after 11 weeks' treatment. Two patients remained proteinuric despite continuing treatment with cyclosporin A, but control of sodium balance was easy and serum albumin concentrations remained higher than without cyclosporin A. In all patients renal function improved during treatment.

These preliminary results show that cyclosporin A may be effective in the treatment of patients with nephrotic syndrome that resists every other form of treatment and especially in the treatment of those with minimal change lipoid nephrosis. The results are in keeping with a T lymphocyte mediated mechanism of minimal change lipoid nephrosis and focal

segmental glomerulosclerosis, but they also suggest that minimal change lipoid nephrosis and focal segmental glomerulosclerosis are separate entities.

Introduction

Nephrotic syndrome of minimal change lipoid nephrosis and of focal and segmental glomerulosclerosis follows an unpredictable course with corticosteroid treatment.^{1,2} Many patients relapse more than once, some are or become resistant to corticosteroids, and some are dependent on corticosteroids. Patients with nephrotic syndrome who are dependent on corticosteroids require permanent corticosteroid treatment with its attending hazards. Cytotoxic drugs may induce remissions,³ but their use is marred by the risks of opportunistic infections, sterility in men, and development of malignancies. In patients who are resistant to any treatment the chronic development of nephrotic syndrome is a debilitating condition, dangerous superinfections may occur, and focal segmental glomerulosclerosis may lead to end stage renal failure.⁴

Idiopathic nephrotic syndrome may be due to secretion of a substance that modifies glomerular anionic charges,^{5,6} and this substance may be a lymphokine.⁷ We therefore undertook an open therapeutic trial of treatment with cyclosporin A alone in six nephrotic patients (three with minimal change lipoid nephrosis and three with focal segmental glomerulosclerosis) for whom we thought we had reached a therapeutic dead end.

Patients and methods

Adult patients were selected according to resistance to or dependence on corticosteroids. The diagnosis of minimal change lipoid nephrosis or focal segmental glomerulosclerosis was confirmed by at least one renal biopsy specimen comprising a minimum of 10 glomeruli, studied by light microscopy and immunofluorescence and conforming to established criteria.¹ Resistance to corticosteroids was defined by proteinuria (at least 2 g/24 hours) persisting after three months of treatment with at least 1 mg prednisone/kg body weight/24 hours and dependence on corticosteroids by relapse when dosage was gradually reduced to 20 mg/day. Any treatment

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that was being taken for nephrotic syndrome was interrupted (cytotoxic agents four months and corticosteroids at least 15 days before the start of the trial).

During the first 18 days of the trial the patients were given a placebo (oil and solvent), and urinary protein was measured twice a week for two weeks and daily for the last three days. After checking that nephrotic syndrome was still present (excluding spontaneous remission), we gave the patients cyclosporin A at an initial dosage of 5 mg/kg body weight/day in two divided doses. Whole blood cyclosporin A concentrations were measured by radioimmunoassay twice weekly before the morning dose, and dosage was

at about 125 ng/ml. In the other patient with minimal change lipid nephrosis (case 2) remission was observed after 35 days of treatment, but she relapsed when cyclosporin A treatment was stopped because of pregnancy. Cyclosporin A treatment was resumed four months after she had aborted spontaneously. A second course of cyclosporin A yielded remission within 35 days of treatment. From then on, despite increasing dosage, cyclosporin A blood concentrations diminished steadily, resembling enzymatic induction. She relapsed when blood concentrations fell below 125 ng/ml. Dosage was increased to 1000 mg/24 hours, blood concentration rose to 780 ng/ml, and proteinuria regressed again.

FIG 1—Woman (case 1) aged 59 with minimal change lipid nephrosis had corticosteroid-resistant nephrotic syndrome. Cyclosporin A induced complete remission within 42 days. She relapsed soon after end of treatment and remitted rapidly when cyclosporin A treatment was resumed. At day 135 of second course dose was reduced gradually to nothing, but nephrotic syndrome reappeared when cyclosporin A blood concentrations were below 125 ng/ml. She became cyclosporin dependent and renal tolerance became excellent, perhaps because of low blood concentrations of cyclosporin A.

Conversion: SI to traditional units—Serum creatinine: 1 $\mu\text{mol/l}$ $\approx$ 0.01 mg/100 ml.

adjusted to obtain trough concentrations between 150 and 750 ng/ml. After six weeks blood concentrations of cyclosporin A were monitored once weekly. Each week blood and 24 hour urine specimens were collected for the following tests: creatinine clearance, 24 hour protein and sodium excretion, serum protein electrophoresis, liver tests, fibrin split products in blood and urine, and complete blood count. Informed consent was obtained from all patients.

Case reports

The case reports of the six patients are summarised in table I. Nephrotic syndrome had developed over 3.5 to 23 years in the patients with minimal change lipid nephrosis. All had responded at some time to treatment with corticosteroids but had developed resistance or dependency. Their renal function was always normal. In the three patients with focal segmental glomerulosclerosis nephrotic syndrome had developed over four to six years. One had been resistant to corticosteroids from the onset of nephrotic syndrome, the two others had responded for some time to corticosteroids and immunosuppressive treatment. They all had severe nephrotic syndrome and mild renal insufficiency when the trial was undertaken.

Results

Table II and figs 1 and 2 summarise the results. In two patients (cases 1 and 3) with minimal change lipid nephrosis complete remission was obtained within 12 to 42 days. Both patients relapsed when cyclosporin A was withheld at 90 days and both responded rapidly to resuming treatment. From then on they were cyclosporin dependent with a threshold of efficacy

In contrast, the three patients with focal segmental glomerulosclerosis had only partial remission. One died of myocardial infarction at 11 weeks. In the two others severe relapse was observed when cyclosporin A treatment was stopped at 90 days; proteinuria diminished appreciably when treatment was resumed. Subsequently, one patient (case 5) excreted 1.4 g of protein/24 hours and serum albumin concentration was 3.8 g/dl.

TABLE I—Clinical features of six patients with nephrotic syndrome treated with cyclosporin A

Case No	Sex	Year of birth	Year of onset of nephrotic syndrome	No of renal biopsy examinations	Lesion	Previous treatment
1	F	1923	1982	1	Minimal change lipid nephrosis	Prednisone
2	F	1959	1980	2	Minimal change lipid nephrosis	Prednisone, cyclophosphamide
3	M	1940	1962	4	Minimal change lipid nephrosis	Prednisone, cyclophosphamide
4	M	1923	1979	2	Focal segmental glomerulosclerosis	Prednisone, cyclophosphamide, chlorambucil, plasma exchange
5	M	1959	1979	2	Focal segmental glomerulosclerosis	Methylprednisolone,* prednisone, cyclophosphamide
6	F	1954	1982	3	Focal segmental glomerulosclerosis	Prednisone

*Boluses given intravenously.

TABLE II—Data on six patients with idiopathic nephrosis treated with cyclosporin A

	Case No					
	1	2	3	4	5	6
Average maintenance dosage of cyclosporin A:						
mg/day	150	500	140	300	100	250
mg/kg/day	3	8	2.2	5	2	3.5
Whole blood trough cyclosporin A (ng/ml):						
Minimum	125	98	280	270	350	250
Maximum	265	780	1060	310	1375	510
Serum creatinine (μmol/l):						
Initial	106	97	98	147	224	141
Final	102	62	79	104	147	87
Creatinine clearance (ml/min):						
Initial	70	66	80	66	37	50
Final	72	138	96	95	55	75
24 h urinary protein (g):						
Initial	9.75	15	9	20	8	12
Final	0	0	0	3	1.4	4
Time between start of treatment and nadir of proteinuria (days)	42	35	12	15	20	20

Conversion: SI to traditional units—Serum creatinine: 1 μmol/l=0.01 mg/100 ml.

Interestingly, in all patients, even in those in whom remission was partial, sodium diuresis was observed before proteinuria had declined appreciably and all were free of oedema as long as treatment was maintained.

Discussion

The results of this trial confirmed our hypothesis that cyclosporin A may induce remissions in patients with idiopathic nephrotic syndrome in whom other treatments have failed. The response differed in three patients with minimal change lipid nephrosis, in whom total remission was obtained, and in those with focal segmental glomerulosclerosis, in whom remission was partial—that is, where proteinuria did not resolve completely.

In patients with glomerular disease with heavy proteinuria and hypoalbuminaemia the mechanism, evolution, and nosology of minimal change lipid nephrosis and focal segmental glomerulosclerosis remain unclear. Increased glomerular permeability to proteins contrasts with the absence or paucity of glomerular lesions, and loss of fixed negative charges may make the glomerular capillary structures less anionic, thus allowing increased passage of the negatively charged serum albumin into Bowman’s space. The loss of negative charges appears to be a generalised phenomenon.⁸ Thus a humoral factor may interfere with electronegativity of the cell membrane. Despite contradictory data many reports have suggested the secretion of a lymphokine.⁹ Idiopathic nephrosis is also attended by an imbalance in T suppressor and T helper lymphocyte subpopulations and by other abnormalities that, together with the favourable effect of cytostatic agents, also support a disorder in cellular immunity causing nephrotic syndrome.⁹⁻¹⁵ Consequently, it seemed logical to try to treat patients with nephrotic syndrome that resisted all other forms of treatment with cyclosporin A as this drug interferes with the production of interleukin 2 and of other lymphokines.¹⁶⁻¹⁸ The favourable response in all our patients, albeit partial in those with focal segmental glomerulosclerosis, could be taken as further evidence that a lymphokine is responsible for nephrotic syndrome in cases of minimal change lipid nephrosis and focal segmental glomerulosclerosis.

Interestingly, urinary sodium excretion reappeared before proteinuria had noticeably diminished. At this time serum total protein and serum albumin concentrations were unchanged and there was no reason to believe that blood volume had increased, thereby promoting natriuresis. Renal function was stable, and we reject the hypothesis that tubular toxicity of cyclosporin A induced sodium wasting. In laboratory animals and in man sodium retention of nephrotic syndrome is due to some intrarenal mechanism rather than to the renin-angiotensin-aldosterone system.^{19,20} The same chronology between onset of natriuresis and delayed regression of proteinuria has been noted with treatment with corticosteroids.²¹

We therefore hypothesise that cyclosporin A “uncoupled” two components of sodium retention in nephrosis: one directed towards intrarenal mechanisms of sodium retention, the other acting on glomerular permeability to proteins.

The nosology of minimal change lipid nephrosis and focal segmental glomerulosclerosis remains a matter of debate. Many nephrologists are convinced that these are but two facets of the same illness.²² Unfortunately, in the absence of any biological marker their opinion rests more on evolutive arguments than on other grounds. Thus the differing responses of our three patients with

FIG 2—In three patients with focal segmental glomerulosclerosis cyclosporin A induced partial remission with appreciable rise of serum albumin concentrations. One patient (---) died of myocardial infarction. In the two others state of partial remission at one year depended on maintenance of treatment with cyclosporin A. In all three renal function improved after treatment.

minimal change lipid nephrosis, in whom proteinuria resolved, as opposed to the partial or transitory remission in the three with focal segmental glomerulosclerosis could support the idea that these glomerular lesions are due to separate mechanisms. Alternatively in focal segmental glomerulosclerosis cyclosporin A may suppress the “functional” part of proteinuria but may leave its “organic” component unchanged because of the focal sclerotic lesions of the glomerular tufts.

This trial shows for the first time that cyclosporin A is active in cases of nephrotic syndrome in which every other treatment has failed. It also shows that proteinuria reappears or increases when cyclosporin A treatment is stopped. Long term tolerance has yet to be evaluated, as this drug may cause renal toxicity. In this series renal and hepatic tolerance was good, perhaps owing to scrupulous monitoring of whole blood trough concentrations and avoiding concentrations persistently greater than 750 ng/ml. Nevertheless, one of our patients died from a coronary accident two months after starting this treatment. Hypercoagulability is a known complication of nephrotic syndrome, and the observations of Vanrenterghem *et al* indicate that cyclosporin A increases the incidence of thrombosis

in transplant recipients.²³ Because of the potential risk of such complications anticoagulation or platelet antiaggregants, or both, should be prescribed systematically to patients treated with cyclosporin A for nephrosis.

Moreover, and this was especially obvious in those with minimal change lipid nephrosis, patients with nephrotic syndrome treated with cyclosporin A become cyclosporin dependent. We do not know how to avoid relapses when treatment is stopped nor the risks of continuing treatment for several years. These crucial issues call for future studies on a larger scale and with controlled methodology.

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100 YEARS AGO

The English climate, although extraordinarily variable within narrow limits, is in the main mild and equable, free from great extremes of temperature, and not characterised by any striking contrasts of season. We cannot count confidently upon heat in July, nor upon frost in December. The cutting blasts of May have ere now made it the most trying month in the year, despite the rhapsodies of the poets, and not rarely January possesses a mildness more appropriate to September. From such peculiarities of climate has sprung the fact that, in the regulation of food, clothing, and habit of life, we take comparatively slight notice of change of season, and frequently neglect climatic indications which are not sufficiently patent to thrust themselves importunately upon our notice. Hence the Englishman is conservative in matters of food and dress. Even when he turns colonist, and becomes a permanent resident in tropical or subtropical lands, he adheres to his ancestral customs, and eats plum-pudding upon Christmas Day in Australia, and drinks bottled Bass's ale in Calcutta, regardless of consequences.

Yet it cannot be doubted that a due regard to season and a prudent adaptation of individual habit to climatic conditions would materially lower our death-rate, and augment the happiness and usefulness of human life among us. The mortality-returns of our winter months are swollen mainly by diseases due to exposure, such as bronchitis and rheumatism; and their prevalence in each class of society is, to a very large extent, proportionate to its ability or inability to protect itself against the vicissitudes of weather. The adoption by all classes during the winter months of underclothing composed of a material like flannel, which maintains a fairly equal temperature of the body, absorbs perspiration, and hinders chill, would do much to promote health and avert disease. This is in every way preferable to the use of heavy overcoats or other outer garments, which are liable to be hastily cast aside, or not to be at hand when required. Specially to be deprecated is the use by delicate women of sealskin-jackets, which enjoy much popularity from their handsome appearance, and the luxurious sensations which they confer upon the wearer. They are objectionable, because our average winter weather is far too mild and open to demand the constant use of furs of any kind, which are appropriate enough to the winter rigours of Minnesota or Winnipeg; they envelope the wearer in a close overheated atmosphere, hindering the exhalations of the body, and strongly predisposing to chill; they are too heavy to be easily borne, and, consequently, they tend to limit healthful exercise. On all these grounds, we think the profession would act wisely in discouraging their general adoption by the wealthy classes as their appropriate winter attire.

The condition of the feet calls for attention in winter, as the constant wet of our streets penetrates through ordinary boots, and produces a damp and chilly sensation. This may be guarded against by the use of waterproof overshoes, of inside linings, or equally well by always keeping two or three

pairs of boots in constant use, and changing them frequently, according to the state of the weather and the condition of the streets.

The hands should be covered in winter while the individual is out of doors, and, if subject to chilblains, he should recollect that this troublesome affection owes its origin to deficient circulation of the blood, and must be combated by maintaining the warmth of the affected parts. (*British Medical Journal* 1886;ii:214.)

To grumble is the privilege of an Englishman; and it would seem that sometimes, and especially where vested interests exist, the act of grumbling in itself affords some consolation, and obviates the necessity for more overt measures. How much time is lost, and how much discomfort daily endured, by reason of the cupidity and the lax regulations of railway companies, who shall say? An ingenious writer estimated, for the edification of the Social Science Congress, not long ago, how much time was lost in the aggregate by the unpunctuality of trains; but who shall estimate how much health is lost through the misdeeds of railway companies? the traveller is submitted to the influence of a number of injurious influences, which might be easily removed, were the companies less given over to a shortsighted policy, penny wise and pound foolish. The Londoner, dragged underground through unventilated tunnels, where he is poisoned by noxious gases and choked by sulphurous fumes, is flung out, to wait for an unpunctual connecting train, on some draughty platform, where he is stunned by the clamorous banging of doors, and deafened by the piercing shrieks of unnecessary whistles. No wonder that he arrives at his suburban home jaded and tired, not merely by the legitimate labour of the day, but by these altogether unnecessary annoyances, inflicted because a railway company will not provide suitable engines, adequate brake-power, and well-built carriages, or because a penny is turned by leaving railway-stations unrepaired, and letting off railway-arches to persons engaged in noxious trades. A story is told of one large junction in the outskirts of London, where the booking-clerks, for want of a fireplace, light a fire on the floor of their office, filling the booking-office and its approaches with coal-smoke, to the great distress of at least the more delicate passengers. That these various sources of present discomfort and eventual ill-health may be easily obviated, is clearly shown by the vast superiority of the lines which run out of the north of London over those which run into the southern districts or circulate in London itself. Perhaps it may be thought that the position in the share-lists may afford an explanation in some cases. That there is some relation of cause and effect, is probable; for there must be many who are deterred from venturing to live in some of the southern and eastern suburbs, by the long list of dangers and discomforts to which they would be thereby exposed. (*British Medical Journal* 1886;ii:897.)