Case Report

Tacrolimus treatment for steroid- and cyclosporin-resistant minimal-change nephrotic syndrome

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Introduction

Minimal-change glomerulonephritis (MCGN) is the most frequent cause of nephrotic syndrome in children, while in adults only 25% of all nephrotic syndromes are caused by MCGN [1]. Treatment with steroids causes a partial or complete remission in the large majority of patients with MCGN. Alkylating immunosuppressive drugs such as cyclophosphamide and chlorambucil have been used with some success in steroid-resistant patients [1]. Although cyclosporin A is very effective in the treatment of steroid-dependent MCGN, a remission in steroid-resistant cases can only be achieved in about 60% [2].

We report the case of a young woman with a steroid and CsA-resistant nephrotic syndrome due to a minimal-change glomerulonephritis, who was treated successfully with tacrolimus (FK 506).

Case report

In June 1993 a young woman was referred to our hospital because of the third relapse of a minimal-change nephrotic syndrome. One year previously the patient had been treated in another hospital because of a nephrotic syndrome with oedema, dyspnoea, massive proteinuria and hypoproteinaemia (serum protein 47 g/l, serum albumin 11.3 g/l). Under the tentative diagnosis of minimal-change glomerulonephritis a therapy with 80 mg prednisolone per day was initiated; this led to a normalization of protein excretion. During the next 2 months the steroid dose was tapered stepwise. When reaching a daily dose of 20 mg prednisolone the first relapse occurred. Renal biopsy confirmed the diagnosis of minimal-change glomerulonephritis and 80 mg prednisolone again led to an immediate cessation of proteinuria. Another 2 months later, after tapering steroids to 20 mg prednisolone per day, proteinuria again became manifest. Even with 150 mg prednisolone per day the increasing proteinuria could not be reversed. The patient developed massive oedema, pleural effusions and finally pulmonary oedema, associated with a gain of body weight of 25 kg despite the administration of high doses of loop diuretics. A maximum of urinary protein excretion of 62 g per day was measured. Laboratory tests showed a reduced serum protein of 37 g/l (normal range 66–87 g/l) and a reduced albumin of 24.8 g/l (normal range 35–52 g/l). Administration of intravenous albumin to maintain the oncotic pressure was without effect. Finally a therapy with chlorambucil (7 mg per day for 2 weeks, stepwise dose reduction over 2 more weeks) in addition to fluocortolone (100 mg per day, stepwise reduction to 20 mg per day over 4 weeks) was started. During this treatment proteinuria decreased to 69 mg per day and the patient was discharged with normal serum protein levels and without oedema.

Seven months later the patient presented at our hospital for the first time.

She had increasing oedema of the face and the legs, worsening weakness, nausea and vomiting for 3 days. At the time of presentation the patient was still on a therapy with 20 mg fluocortolone per day. Physical examination showed a patient with normal weight (165 cm, 62.6 kg), with regular heart rate and a blood pressure of 120/70 mmHg. The face and the legs were oedematous, while no clinical signs of ascites were evident. The laboratory tests revealed the pattern of a nephrotic syndrome with the serum protein concentration lowered to 44.4 g/l, albumin lowered to 16.6 g/l, serum cholesterol elevated to 418 mg%, and a proteinuria of 15 g per day. Renal function was normal as judged from normal values for creatinine and urea. Ultrasound investigation revealed kidneys of normal length and structure, ECG, echocardiography and chest X-ray were normal as well. Both laboratory findings and physical examination were not indicative of vasculitis or rheumatic disease. A renal biopsy including an electron-microscopic evaluation confirmed the diagnosis of minimal-change glomerulonephritis without focal or segmental glomerular sclerosis.

Administration of 60 mg methylprednisolone decreased the proteinuria to normal values. Because...
all relapses had occurred while the patient was still on a therapy with relative high doses of steroids (= steroid-dependent MCGN), a combination therapy with cyclosporin (whole blood concentrations of about 100 ng/ml) and prednisolone was started. Again the steroid dose was reduced in a stepwise manner and stopped in November 1993. Except for a gastritis with haematemesis, no medical problems occurred in the following year, so that the CsA dose was reduced and finally stopped as planned to reduce the risk of CsA nephrotoxicity in August 1994. Two weeks after the cessation of the immunosuppressive therapy the patient developed the fourth relapse, which could be suppressed by the immediate restarting of the therapy with cyclosporin and prednisolone. Again plasma creatinine and urea were in the normal range. During the following year, using this therapy, a complete remission was achieved, complicated by nausea and occasional vomiting after taking CsA. In August 1995, with the patient at 27 years of age, the fifth relapse occurred while still on therapy with CsA, presenting with proteinuria of 8 g/l, an increase of body weight of 10 kg and orthopnoea. An increase of the steroid dosage to 80 mg per day did not affect the proteinuria and the short-term intravenous administration of 240 mg frusemide in addition to 25 mg hydrochlorothiazide p.o. per day led to no mobilization of the oedema. During this high-dose diuretic therapy an increase of creatinine (to 1.94 mg% (0.5–0.9 mg%)) and urea (to 142 mg% (10–50 mg%)) was observed for the first time. Because of steroid- and CsA-resistant nephrotic syndrome, CsA was replaced by tacrolimus (FK 506). With a daily dosage of 6 mg tacrolimus, attaining whole-blood concentrations of 5–7 μg/l, in combination with a daily dose of 50 mg prednisolone, the proteinuria decreased within 10 days to normal values; in addition serum creatinine and urea decreased to the normal range again. Until December 1995 the dosage of prednisolone was reduced to 5 mg per day, and in April 1996 the steroid therapy was stopped completely. Since the beginning of the therapy with tacrolimus no more episodes of nausea or vomiting nor other side-effects have been observed.

In September 1996, after 1 year of treatment with tacrolimus, a further renal biopsy was performed. Histological findings were consistent with a minimal-change glomerulonephritis in complete remission. No signs of tubular damage attributable to cyclosporin, tacrolimus, or FSGN was seen. Currently the patient feels well and is in excellent physical shape. The nephrotic syndrome remains in complete remission and the renal function is normal. With a daily dosage of 4 mg tacrolimus a therapeutic whole-blood level of about 5 μg/l is maintained.

The case of this young lady was discussed briefly in a letter to The Lancet [7].

Discussion

The therapeutic strategy in minimal-change nephrotic syndrome comprises steroids, and in steroid-resistant cases cyclosporin, azathioprine, and alkylating agents like cyclophosphamide or chlorambucil [1–3]. Our case documents the successful treatment of steroid- and CsA-resistant minimal-change glomerulonephritis with tacrolimus (Figure 1).

Tacrolimus (FK 506) is a macrolide antibiotic which is isolated from the fungus Streptomyces tsukubaensis. Very similar to cyclosporin, tacrolimus has a relatively selective inhibitory action on CD4 T helper lymphocytes. Although both drugs prolong solid-organ allograft survival, as shown in several studies, tacrolimus seems to have superior immunosuppressive effects [4,5]. There is evidence from the literature to suggest a superior proteinuria control with tacrolimus com-
compared to cyclosporin in for example focal sclerosing glomerulonephritis of native and grafted kidneys [6,7].

One possible explanation for superior effects of tacrolimus compared to CsA in the treatment of nephrotic syndrome might be the more potent effect on release of cytokines. Garin and Chandler [8] demonstrated that the proteinuria in minimal-change glomerulonephritis is mediated by IL-8 since anti-IL-8 antibodies could suppress proteinuria. Thus a stronger suppression of IL-8 by tacrolimus could result in a better effectiveness with regard to proteinuria. Another possible explanation could be the suppressive effect on the production of vascular permeability factor (VPF). Maruyama et al. [9] demonstrated a significant inhibition of the production of VPF by tacrolimus in T lymphocytes cultured from patients with MCGN nephrotic syndrome. In comparison to results obtained with cyclosporin this effect of tacrolimus occurs at much lower concentrations, e.g. similar effects were reached using a tacrolimus concentration of $10^{-10}$ M in contrast to a concentration of $2 \times 10^{-7}$ M of cyclosporin [9,10].

This case report emphasizes the potential of a successful treatment of steroid- and CsA-resistant minimal-change nephrotic syndrome with tacrolimus over 20 months without any obvious side-effects.

References


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