Case Report

Combination therapy with sirolimus (rapamycin) and tacrolimus (FK-506) in treatment of refractory minimal change nephropathy, a clinical case report

Preeti Patel, Suvankar Pal, Caroline Ashley, Paul Sweny and Aine Burns

Department of Renal Medicine, Royal Free Hospital, Pond St, London NW3 2QG, UK

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Introduction

Minimal change nephropathy (MCN) is the dominant cause of idiopathic nephrotic syndrome in childhood and accounts for ~25% of cases of adult nephrotic syndrome [1]. Each new episode of nephrotic syndrome adversely affects quality of life and is associated with complications including infection, thromboembolism and urinary loss of binding transport proteins. Proteinuria usually remits with high dose corticosteroid treatment; however, a significant minority responds incompletely or relapses frequently, providing a difficult therapeutic challenge. Furthermore, the management of frequent relapses with multiple courses of corticosteroids is associated with appreciable morbidity, including muscle atrophy, skin fragility and growth retardation. We report the use of sirolimus (rapamycin) in combination with tacrolimus (FK-506) to induce and maintain remission successfully in a case of chronic resistant MCN. To our knowledge, this is the first report of sirolimus/tacrolimus combination therapy in the treatment of MCN.

Case

A 24-year-old female with resistant relapsing MCN was successfully initiated on combination therapy with sirolimus and tacrolimus to induce and maintain remission of disease. Following initial presentation with nephrotic syndrome at the age of 5 years (September 1985), her childhood disease was characterized by multiple relapses (identified by significant proteinuria ++++ on urine dipstick) despite regular maintenance oral steroids. A course of levamisole (2.5 mg/kg), aged 12, was abandoned due to the adverse reaction of severe dermatitis and failure to sustain disease remission. The diagnosis of minimal change was confirmed histologically on renal biopsy aged 15. Following successive relapses, combination therapy of oral steroids and cyclosporin (5 mg/kg/day) was initiated aged 16. This regime proved unsuccessful and, despite concerns regarding adverse effects on fertility, a 7-week course of oral cyclophosphamide (2 mg/kg/day) was administered. A 2 year period of disease remission followed until a major relapse, aged 18, which was complicated by septic shock (August 1998). Once again, remission was achieved with high dose steroid therapy. Tacrolimus was initiated (3 mg twice daily) in a further attempt to introduce a steroid-sparing immunosuppressive regime (October 1998). Steroid therapy was gradually withdrawn, and she was maintained on tacrolimus monotherapy (2 mg every morning and 1 mg every evening), which was continued until the development of a left retinal vein thrombosis aged 21 (August 2001). The venous thrombosis was attributed to the proliferative effects of tacrolimus on endothelial cells, as there was no haematological evidence of a procoagulant tendency and it occurred during a period of complete disease remission. Soon after, disease relapse occurred and high dose steroid therapy was started once more. Sirolimus monotherapy was initiated (5 mg) in October 2001. This regime predisposed to recurrent upper and lower respiratory tract infections and urinary tract infections. In an attempt to reduce the dose of sirolimus, combination therapy with tacrolimus was initiated 15 months later (sirolimus 2 mg and tacrolimus 2 mg every morning and 1 mg every evening) (January 2002). Disease remission has been sustained for 36 months on this regime and has allowed the patient to complete

Correspondence and offprint requests to: Dr A. Burns, Centre for Nephrology and Transplantation, Royal Free NHS Trust, Pond St, London NW3 2QG, UK. Email: aine.burns@royalfree.nhs.uk

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her university education and pursue full-time employment. Mean tacrolimus levels during this period have been maintained at 5.5 mg/ml and mean sirolimus levels at 8 mg/l. Creatinine clearance as calculated using the Cockcroft and Gault formula has remained stable throughout the disease (between 80 and 100 ml/min). Her recent cholesterol is within range at 4.0 mmol/l with no lipid-lowering agent employed.

Discussion

MCN is associated with a variety of immunological abnormalities affecting both humoral and cell-mediated immunity. T-cell activation and resultant cytokine-mediated injury to the glomerular epithelial foot process has been identified as a major contributor to the pathogenesis of proteinuria. In particular, a type-2 cytokine response has been implicated, dominated by production of interleukin IL-4 and IL-12 and class switching of B cells to production of IgG4 and IgE [2]. The observation that disease activity may be triggered by atopy supports the association with a type-2 cytokine response [2,3]. The humoral nature of the disease is supported by successful renal transplantation from a donor with MCN [4].

The treatment goal in MCN is to induce prompt disease remission and decrease the frequency of relapse whilst minimising complications and adverse events. Until the mid-1980s, the only therapies of proven efficacy were corticosteroids and cytotoxic agents. Whilst these therapies induce disease remission in the majority of cases, prolonged and recurrent use is associated with significant adverse side effects, including osteoporosis, growth retardation, Cushing’s syndrome, weight gain, diabetes and hypertension. Furthermore, in a significant minority, disease remission is not achieved with these agents and refractory relapsing disease provides a significant therapeutic challenge. Other agents employed with variable success include cyclosporin, levamisole, tacrolimus and mycophenolate mofetil [5]. No previous case reports or trials have been published to date describing the use of sirolimus alone or in combination with tacrolimus in treatment of MCN. Considering its lack of nephrotoxicity and its efficacy in transplantation, sirolimus appears an appealing therapy. In addition to being a corticosteroid-sparing regime, combination therapy of tacrolimus with sirolimus allows dose reduction of tacrolimus and reduced risk of iatrogenic nephrotoxicity. Sirolimus acts by inhibiting progression of the cell cycle from G1 to S phase by blocking several signal transduction pathways (the second phase of T-cell activation) [6]. Thus, unlike cyclosporin and tacrolimus (which block the production of cytokines), sirolimus blocks cytokine signal transduction. The most common side effect of sirolimus is hyperlipidaemia, which may exacerbate the adverse lipid profile of nephrotic syndrome resulting in accelerated atherosclerosis and contributing to progressive glomerular injury. In addition, immunosuppression with sirolimus predisposes to recurrent infections as experienced by the patient in this case study, an adverse effect potentially mediated by drug-induced leukopenia. Of note, fulminant de novo focal segmental glomerulosclerosis (FSGS) has been observed in a small series of renal transplant patients treated with sirolimus [7]. Furthermore, Fervenza et al. have recently reported acute renal failure related to low dose sirolimus usage (5 mg/day) in six out of a series of 11 patients with either focal segmental glomerulosclerosis, IgA nephropathy, membranous nephropathy or membranoproliferative glomerulonephritis. In four of these patients, renal function recovered after cessation of sirolimus [8]. Combination therapy with tacrolimus and sirolimus appears to allow reduced doses of both agents to be employed, thus minimizing adverse side effects of both drugs.

Despite advances in conventional treatments during the past two decades, MCN remains a challenging and complex disease. Gene polymorphisms recently have been associated with disease pathogenesis, and it has been suggested that screening for such polymorphisms may indicate response to steroid therapy and aid in selection of the most appropriate therapies [9]. Whilst it is acknowledged that MCN follows a relapsing and remitting course, this case report describes a durable 36 month period of remission achieved whilst on a combination regimen of low dose tacrolimus and sirolimus. We therefore suggest this case attracts attention to a new therapeutic strategy that may foster trials on a larger scale.

References


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