Mycophenolate Mofetil in Minimal Change Nephrosis

R Alfred, AK Soyibo

INTRODUCTION

The use of mycophenolate mofetil in the treatment of steroid resistant minimal change disease has not been extensively studied, particularly in the African Caribbean population. This drug has fewer side effects than most immunosuppressants. On this basis, it may be preferred by both patient and physician. This case report highlights its use in a patient with minimal change nephrosis.

CASE PRESENTATION

A 16-year old female student, with a history of mild intermittent asthma was otherwise well until she presented with a two month history of progressive leg swelling. She had a normal appetite and micturition and bowel motions were also reported as normal. Her menstrual period was also normal.

She complained of severe leg and facial swelling with increasing abdominal girth, despite dietary sodium and fluid restrictions.

She had no rashes, arthralgia or loss of hair. There was no family history of collagen vascular disorders or renal disease, and was on no illicit drugs or non-steroidal anti-inflammatory agents. She presented to another institution and was started on Captopril 25 mg orally, three times daily, furosemide 120 mg orally twice daily and ranitidine 150 mg orally twice daily and then referred to the tertiary hospital for renal biopsy which revealed minimal change disease. Subsequent to this, the patient was started on high dose oral steroids and had repeated admissions for generalized body swelling, despite the use of high dose steroids for four months and two courses, 3 days of each, intravenous methylprednisolone pulses with salt poor human albumin therapy. Physical examination revealed a normotensive female (weight 229 pounds and height 173.5 centimetres) with anasarca and no clinical stigmata of collagen vascular disease. Cardiovascular examination was normal. There was evidence of ascites, with no organomegaly. She exhibited no lateralizing signs.

On initial diagnosis, the 24-hour urine protein was 10.28 g/24 hours with creatinine clearance 100.54 ml/minute. There were no casts seen on urinalysis. Serum analysis showed hyperlipidaemia (total cholesterol 12.4 mmol/L) and hypoalbuminaemia (21 g/L). Liver transaminase levels were normal. Human Immunodeficiency Virus and hepatitis A and B serology, as well as the antinuclear antibody levels were negative. The spot urine to creatinine ratio was 12.39 g/ 24 hours. Abdominal ultrasound revealed normal kidney sizes (right – 10.2 cm, left – 10.9 cm).

Treatment included slow, careful diuresis with a 5-day cocktail of intravenous furosemide (160–320 mg), intravenous albumin (25 g/dL) and aminophylline (250 mg), as well as an angiotensin converting enzyme inhibitor (captopril), a thiazide diuretic (metalazone), a statin (simvastatin) and prophylactic heparin. Her renal function was monitored daily and diuresis tapered as needed. The patient and her parents refused the use of cyclophosphamide because of its potential side effects of infertility and malignancy. Mycophenolate mofetil was offered as the next available choice, particularly as it was also more readily available. A starting dose of 500 mg once daily was eventually titrated to one gram thrice daily over a 3-week period with no side effects. Prednisone was also tapered from 60 mg to 20 mg once daily. Her discharge weight after five weeks of this therapy was 146 pounds and spot urine protein to creatinine ratio was 8.86 grams per 24 hours. After six months of therapy, two repeated spot urine protein to creatinine ratios were 1.01 gram and 0.56 grams per 24 hours.

DISCUSSION

The nephrotic syndrome is defined by a urinary protein level exceeding 3.5 g per 1.73 m^2 of body-surface area per day. Protein leakage is caused by a loss of the negative charge of the glomerular basement membrane, leading to albuminuria. Initially, it was thought that proteinuria led to decreased oncotic pressure and thereby sodium and fluid retention. Current observations reveal a "circulatory overfilling" in this disorder, rather than "underfilling". Subjects studied have been found to have normal or increased plasma volume (1). Sodium retention is seen before proteinuria and hypoalbuminuria develop during relapse, whereas natriuresis occurs before proteinuria is reversed, as seen in the above case (2, 3). Although she lost a significant amount of weight, there was still marked proteinuria, which we hope will respond to long term mycophenolate mofetil. Pharmacologic blockade of the renin-angiotensin-aldosterone system may not cause natriuresis, as one would expect if sodium retention were the result of a compensatory activation of this system (4). In addition, increased levels of atrial natriuretic peptide have been demonstrated experimentally, further supporting the "overfilling" hypothesis behind nephrotic syndrome (5). The

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From Department of Medicine, The University of the West Indies, Kingston 7, Jamaica, West Indies.

Correspondence: Dr R Alfred, Department of Medicine, The University of the West Indies, Kingston 7, Jamaica, West Indies. E-mail: rose24_tt@yahoo.com

use of the aminophylline/furosemide/albumin cocktail makes use of the theory behind the role of the distal nephron in nephrotic syndrome (6). Aminophylline has been found to block sodium retention at the distal nephron in neonates, and furosemide binds albumin in its delivery to its target cells.

Micropuncture studies show unchanged delivery of filtrate to the distal nephron, pointing to increased sodium reabsorption at even more distal sites (7). A further abnormality is the hyporesponsiveness to atrial natriuretic peptide caused by a postreceptor defect (8). Sodium reabsorption distally was also achieved by the use of a thiazide in this case.

Mycophenolate mofetil is an immunosuppressive agent that inhibits purine biosynthesis of B and T lymphocytes. Its main use has been proven in transplantology. Other trials have demonstrated its use in membranous nephropathy and focal segmental glomerulosclerosis (9, 10). This case shows that it is promising in the management of steroid resistant minimal change disease. In the literature search, no long term, randomized, large scale data was seen regarding its use in minimal change nephrotic syndrome.

In a study (11) from China of 142 children with relapsing nephrotic syndrome from 10 clinical trial centres, patients were randomised to a MMF group and a control group receiving cyclophosphamide.

The total remission rate in the MMF group (95.4%) was significantly higher than that in the control group [81.8%] ($p < 0.01$). MMF was found to be more effective in reducing proteinuria, and improving hypoalbuminaemia, oliguria, hyperlipidaemia, and oedema than cyclophosphamide. MMF was better tolerated with lower incidences of adverse reactions than cyclophosphamide (12).

In conclusion, in a study of children with frequently relapsing nephrotic syndrome it was found that MMF was effective in maintaining remission for at least 6 months and was associated with a low incidence of adverse events. In an adult population study (13), of patients with biopsy proven primary glomerulopathy and who received MMF it was also shown that complete steroid withdrawal can take place in steroid dependent patients with decrease in proteinuria and no increase in serum creatinine.

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