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Mycophenolate Mofetil: Role in the Treatment of Glomerular Disease

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Introduction

Mycophenolate mofetil (MMF) is a specific inhibitor of inosine monophosphate dehydrogenase and a suppressor of both T and B cell lymphocyte proliferation. It has been used successfully for the prevention of acute and chronic rejection of renal allografts. Although MMF has been introduced as an immunosuppressive drug, it has also effects on non-immune cells. It has an antiproliferative action on vascular smooth muscle cells and beneficial effect on chronic graft dysfunction.

These two actions of MMF were noted in glomerular disorders, in experimental and clinical studies.

Experimental studies (1)

MMF was effective in the prevention of progressive nephritis in murine models of SLE and proteinuria in the Heymann membranous glomerulonephritis. Mesangial cell proliferation and differentiation into myofibroblasts was significantly inhibited by MMF as well as proliferation of tubular cells.

Human glomerular diseases (2,3)

- MMF reduces the rate of recurrence of IgA nephropathy in kidney allografts.
- MMF treatment, specially combined with steroids presents remarkable improvement of resistant lupus nephritis without side effects known in cyclophosphamide treatment. MMF leads to a more pronounced reduction of glomerular immune deposits, glomerular necrosis, microthrombus formation and vascular changes.
- MMF might also be useful for the treatment of vasculitis, Wegener,s granulomatosis and microscopic polyarteritis.
- MMF caused improvement of the nephrotic syndrome in membranous nephropathy and idiopathic nephritic syndrome (in childhood)
- A marked decrease in proteinuria was seen in some patients with IgA nephropathy, but taking into consideration the fact that the disease is slow progressive the effect on the outcome is uncertain.

Patients and methods, results

MMF treatment in lupus nephritis

We treated three groups of patients with lupus nephritis: 1)with high histological activity index (AI), 13.4+-2,34, 8 patients, 2)high histological chronicity index (CI) (6+-0,7) 8 patients, and 3)low AI (3,5) and low CI (1,5), two patients. The patients were treated for two years, MMF 2g/daily/prednisone for the first, and MMF/1,5g/daily/prednisone for the second year. Patients with high AI presented significant decrease of serum creatinine after two years 286+-112,95 to 131,2+-44,65, two patients with acute oligoanuria were withdrawn from dialysis treatment. Significant improvement of proteinuria was also noted, from 6,97+-1,81 to 0,9+-0,31g/daily. Patients with high CI presented non-significant decrease of serum creatinine 178,5+-47,73 to 129,25+-22,88, but significant improvement of proteinuria 4,63+-1,57 to 1,14+-0,39g/daily. One patients from the third group presented recovery of the renal function (creatinine 196 to 72) and improvement of proteinuria (7,93 to 3,4g/daily) but the other did not respond.

MMF treatment in membranoproliferative and crescentic glomerulonehritis

5 patients with membranoproliferative glomerulonephritis (MPGN) and 4 with crescentic GN (>80% crescents, non-oliguric form) received MMF for 3 years as primary treatment, 2g/daily for 12 months and 1 g/daily for the further 24 months. Control group consisted of 10 patients with same disorders and cyclophosphamide/steroids treatment. 5 patients with MPGN presented slight, non-significant increase of serum creatinine during follow-up period (97,+_27,22, to 121,6+-41,59) and evident decrease of proteinuria , from 3,96+-0,74 to 1,4+-0,23g/daily. Control group (5 patients) presented also slow increase of creatinine, but the proteinuria remained unchanged: 3,74+-0,65 to 3,09+-0,98g/daily. 4 patients with crescentic GN presented significant improvement of creatinine 431,75+-148,53, to 136+-41,3. 2/5 patients from the control group developed end-stage chronic renal failure.

MMF treatment in idiopathic membranous nephropathy

We performed MMF 2g/daily for 9 months in 8 patients,3 male and 5 female with idiopathic membranous nephropathy, stage III-IV. Previous treatment (steroids, cytotoxic drugs, cyclosporine) had failed in 5/8 patients, MMF was used as first choice drug in the other three patients because of presence of diabetes, type 2, on diet.

Serum creatinine levels presented decrease, 107,9+-15 to 86,6+-11,6. Proteinuria decreased significantly after 3 months, but later it was stable: 4,44+-0,74, 1,99+-0,29, 1,82+-0,32g/daily. Complete recovery of the nephrotic syndrome was not noted.

MMF in focal segmental glomerulosclerosis

MMF treatment was performed for two years, 2 g daily for the first, and 1 g/daily for the second year. The patients presented stable renal function and significant, but not sufficient decrease of proteinuria (6,06+-1,28 to 3,18+-0,74g/daily).

Minimal change nephrotic syndrome

3 patients were treated and presented complete recovery of the nephrotic syndrome, proteinuria 4,7+-2,7 to 0,25+-0,15g/daily.

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Discussion and conclusions

MMF in our patients presented both actions:

- as an immunosuppressive agent it acts in crescentic glomerulonephritis and lupus nephritis and improve renal function and nephrotic syndrome, and a combination of both actions was noted in advanced form of membranous nephropathy, lupus nephritis with high CI and focal-segmental glomerulosclerosis.

MMF may have therapeutic applications beyond immunosuppression in transplant recipients. This is particularly true for immune-mediated glomerular disease. Preliminary results suggest that MMF is effective in several types of glomerulonephritis after conventional therapy had failed. The toxicity of MMF is low compared with cyclophosphamide. As it was mentioned previously, MMF combines two actions: as an immunosuppressive agent it reduces the inflammatory process early on and subsequently it interferes with the genesis of fibrosis. Randomized controlled studies are obviously mandatory to provide definite evidence for the efficacy and safety, and to define indications for treatment.

References

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