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Editorial comment

The Pros and Cons of Use of Cyclosporine-A in Idiopathic Membranous Nephropathy

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Idiopathic membranous nephropathy (IMN) represents the most common cause of nephrotic syndrome in adults characterized by deposition of immune-complexes in the subepithelial area of the glomerulus [1,2]. Patients with persistent and relapsing nephrotic syndrome are at increased risk for progression of renal disease. The risk is higher in patients with deteriorating renal function and proteinuria above 8g/24h and this should be taken in consideration for administration of immunosuppressive treatment [3]. The combination of corticosteroids with cytotoxic drugs [chlorambucil and cyclophosphamide] is followed by frequent remission of nephrotic syndrome at the expense of potential serious adverse reactions [4-6]. Cyclosporine-A (CsA) is a calcineurin inhibitor with immunosuppressive effect due to inhibition of the production of interleukin-2. It has been extensively used in the treatment of proteinuric glomerular diseases and proved to be effective in inducing remission of idiopathic nephrotic syndrome in children and adults [7]. Apart from its immunosuppressive action, CsA exerts an antiproteinuric effect related to vasoconstriction of afferent arteriole and direct action to glomerular permeability [8,9]. Furthermore blocking of calcineurin-mediated dephosphorylation of the actin-organizing protein synaptopodin leading to stabilization of actin cytoskeleton in podocytes represents another mechanism of antiproteinuric effect of CsA [10].

CsA has been used in patients with IMN and nephrotic syndrome resistant to corticosteroids and/or cytotoxic drugs and as initial treatment, in order to avoid the side effects of cytotoxics drugs. The administration of CsA (initial dose 3.5 mg/kg BW/day adjusted to through blood levels between 125 and 225 ng/ml) with low prednisone dose (0.15 mg/kg/day) for 24 weeks in patients with steroid resistant nephrotic syndrome and preserved renal function was found to be more effective in inducing remission of nephrotic syndrome (75% vs. 22%) than the combination of placebo with the same dose of prednisone in a prospective randomized controlled trial [11]. Although relapses were observed in patients with remission of nephrotic syndrome, significantly higher percentage of CsA treated patients remained in remission 12 months after discontinuation of treatment (39% vs. 13%, p=0.007) [11]. CsA was also found to have a beneficial effect in the remission of nephrotic syndrome and preservation of renal function in patients with progressive IMN as it was defined by deterioration of renal function and persistent nephrotic range proteinuria [12].

CsA was given as initial treatment in a small number (n =16) of IMN patients with nephrotic syndrome and well-preserved renal function [13]. All patients received combination of CsA (2-3 mg/kg BW/day, with dose adjusted to target trough blood levels of 100 ng/ml for 18 months and then gradually reduced for six months) and prednisolone (0.5 mg/kg BW/day gradually reduced to 10 mg on alternate days at six months and 5 mg at 12 months). Complete remission of nephrotic syndrome was observed in 8 (50%) and partial remission in 6 (37.5 %) patients [13]. The effectiveness of combination of CsA with prednisolone was recently compared to that of CsA monotherapy (target trough blood levels between 100 and 200ng/ml) [14]. After 6 months of treatment complete remission was observed in 19% of patients treated with combination and in 5% of those treated by CsA monotherapy, whereas partial remission was observed in 64% and 80%, respectively. After 12 months, the rate of complete remission increased in both groups, but remained higher in the combination group (35% vs. 20%). Taken together, 83% and 85% of patients respectively was either in complete or partial remission after 12 months of treatment [14].

The combination of CsA with corticosteroids as initial treatment was compared to the traditional treatment of IMN with corticosteroids and cytotoxic drugs in a large retrospective multicenter study [15]. The total remission rate of nephrotic syndrome was significantly higher in patients treated by CsA (85% vs. 55%, p=0.004) whereas complete remission was observed in 47% and 26% of them respectively. Furthermore, administration of CsA in patients with nephrotic syndrome resistant to steroids and cytotoxic drugs was followed by complete remission in 86% of them. In addition the need for discontinuation of treatment and the risk of side-effects was significantly lower with CsA [15].

Relapses of nephrotic syndrome occur in about 30% of patients with IMN who show remission, either spontaneously or after administration of cytotoxic drugs [1,2] whereas

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frequent relapses have been reported after discontinuation of CsA [7]. It has been proposed that administration of a maintenance dose for a few months after remission and gradual tapering of CsA can reduce the incidence of relapse [16]. A slight higher but not significantly different relapse rate was observed in patients treated with steroids and CsA in gradually reduced dose in comparison to those treated with steroids and cytotoxic drugs (41% vs. 29%, p=NS) [15]. Re-administration of steroids and CsA, after the first episode of relapse, was followed by complete or partial remission in 92% of patients. However, multiple relapses were observed in 28% of patients who showed a gradual unresponsiveness to CsA and deterioration of renal function [15]. It is interesting that a higher relapse rate has been reported with CsA monotherapy than with combination of CsA and steroids (47% vs. 15%) [14]. However, at the time of relapse the mean maintenance dose of CsA and the trough CsA blood levels were significantly lower in patients with relapse (72±48 vs. 194±80 ng/ml, $p<0.03$) [14]. It is of note that a transient increase of serum creatinine, related to CsA dose has been reported in some studies. An increase in baseline serum creatinine by 30% was observed in patients with trough blood levels above 150 ng/ml [11,14] and improvement of renal function was observed after CsA dose reduction. On the other hand no change in renal function and no adjustment of CsA dose were necessary in patients with trough blood levels about 100 ng/ml [13].

CsA is a potentially nephrotoxic drug and characteristic lesions of CsA nephrotoxicity have been described in repeat biopsies of patients with idiopathic nephritic syndrome treated with doses higher than 5.5 mg/kg BW/day [17]. It should also be noted that this cut-off dose has been established with the old form of the drug (Sandimmun), whereas the new one (Neoral), with a better bioavailability, might be toxic in lower doses. Repeat renal biopsies in patients with IMN showed that CsA does not prevent the continuing immune-complexes formation even in patients with remission of nephrotic syndrome [18]. Although no CsA nephrotoxicity was observed in 6 CsA treated patients with relapses of nephrotic syndrome and decline of GFR, increase of glomerular sclerosis and interstitial fibrosis was evident in the repeat renal biopsies [18]. In our recent study repeat biopsies were performed in 18 patients with remission of nephrotic syndrome and well preserved renal function after 24 months of treatment with CsA [19]. Progression of the stage of the disease was identified in 11 patients (61%) and deterioration of glomerulosclerosis and tubulointerstitial injury in 10 out of 18 (55%). These findings were evident in 50% and 43% of patients with 2 years (n=14) and in all patients with more than 5 years duration of the disease (n=4). Apart from isometric vacuolation of tubular epithelial cells in 2 patients, no other signs of CsA nephrotoxicity were recognized. A signifycant correlation of the severity of histological lesions with time elapsed from the first biopsy ($r=0.452$, $p<0.05$) was also observed. These findings suggest that it is probably the natural history of the disease and not CsA, responsible for the development of these lesions. However, an influence of CsA in the deterioration of chronic histological lesions cannot be excluded [20].

In conclusion, the combination of CsA with corticosteroids represents an effective regimen in inducing remission of nephrotic syndrome, in patients with idiopathic membranous nephropathy. However, relapses are frequently observed after CsA withdrawal and long-term treatment is usually necessary. Since CsA is a potentially nephrotoxic drug and repeat renal biopsies show deterioration of chronic histological lesions with time the long-term use should be examined with caution.

Conflict of interest statement. None declared.

References

1. Muirhead N. Management of idiopathic membranous nephropathy: Evidence-based recommendations. *Kidney Int* 1999; 55(Suppl 70): S47-S55
2. Ponticelli C. Membranous nephropathy. *J Nephrol* 2007; 20: 268-287.
3. Cattran DC: Frontiers in Nephrology: Membranous nephropathy. *J Am Soc Nephrol* 2005; 16: 1188-94.
4. Ponticelli C, Zucchelli P, Passerini P, *et al*. A 10-year follow-up of a randomized study with methylprednisolone and chlorambucil in membranous nephropathy. Kidney Int 1995; 48: 1600-04.
5. Jha V, Ganguli A, Saha TK, *et al.* A randomized controlled trial of steroids and cyclophosphamide in adults with nephrotic syndrome caused by idiopathic membranous nephropathy. *J Am Soc Nephrol* 2007; 18: 1899-904.
6. Ponticelli C, Altieri P, Scolari F, *et al.* A randomized study comparing methylprednisolone plus chlorambucil versus methylprednisolone plus cyclophosphamide in idiopathic membranous nephropathy. *J Am Soc Nephrol* 1998; 9: 444-50.
7. Cattran DC, Alexopoulos E, Heering P, *et al*. Cyclosporin in idiopathic glomerular disease associated with the nephrotic syndrome: Workshop recommendations. *Kidney Int* 2007; 72: 1429-47.
8. Guasch A, Suranyi M, Newton L, *et al*. Short-term responsiveness of membranous nephropathy to cyclosporin. *Am J Kidney Dis* 1992; 20: 472-81.
9. Zietse R, Wenting G, Kramer P *et al*. Effects of cyclosporin A on glomerular barrier function in the nephrotic syndrome. *Clinical Science* 1992; 82: 641-50.
10. Faul C, Donnelly M, Merscher-Gomez S, *et al*. The actin cytoskeleton of kidney podocytes is a direct target of the antiproteinuric effect of cyclosporine A. *Nat Med* 2008; 14(9): 931-938.
11. Cattran DC, Appel GB, Hebert LA, *et al*. for the North American Nephrotic Syndrome Study Group. Cyclosporine in patients with steroid-resistant membranous nephropathy: A randomized trial. Kidney Int 2001; 59: 1484-90.
12. Cattran DC, Greenwood C, Ritchie S, *et al*. for the Canadian Glomerulonephritis Study Group. A controlled trial of cyclosporine in patients with progressive membranous nephropathy. *Kidney Int* 1995; 45: 1130-5.
13. Goumenos DS, Kalliakmani P, Tsakas S, *et al*. The remission of nephrotic syndrome with cyclosporin treatment does not attenuate the progression of idiopathic membranous nephropathy. *Clin Nephrol* 2004; 61: 17-24.
14. Alexopoulos E, Papagianni A, Tsamelashvili M, *et al*. Induction and long-term treatment with cyclosporin in membranous nephropathy with the nephrotic syndrome. *Nephrol Dial Transplant* 2006; 21: 3127-32.
15. Goumenos DS, Katopodis K, Passadakis P, *et al*. Corticosteroids and cyclosporin-A in idiopathic membranous

nephropathy: higher remission rate of nephritic syndrome and less adverse reactions than the traditional treatment with cytotoxic drugs. *Am J Nephrol* 2007; 27: 226-31.

16. Ponticelli C, Passerini P. The place of Cyclosporin in the Management of Primary Nephrotic Syndrome. *BioDrugs* 1999; 12: 327-41.
17. Meyrier A, Noël L-H, Aurishe P, Callard P, the Collaborative Group of the Societe de Néphrologie, with the technical assistance of Broneer D. Long-term renal tolerance of cyclosporin A treatment in adult idiopathic nephrotic syndrome. *Kidney Int* 1994; 45: 1446-56.
18. Ambalavanan S, Fauvel JP, Sibley RK, Myers BD. Mechanism of the antiproteinuric effect of cyclosporin in membranous nephropathy. *J Am Soc Nephrol* 1996; 7: 290-8.
19. Kalliakmani P, Koutroulia E, Sotsiou F, *et al*. Benefit and cost from the use of cyclosporine-A in idiopathic membranous nephropathy. *Nephrology* 2010; 15: 762-767.
20. Goumenos DS. What have we learned from the use of ciclosporin A in the treatment of nephrotic patients with idiopathic membranous nephropathy? *Expert Opin Pharmacother* 2008; 9(10): 1695-1704.