

8 Summary

Mycophenolate mofetil slows progression in anti-Thy1-induced chronic renal fibrosis, but is not additive to a high dose of enalapril.

In the present work it was investigated in the animal model of anti-Thy1-induced chronic-progressive glomerulosclerosis of the rat for the first time, whether the progression of the disease and the associated loss of renal function could be attenuated by gavage of an anti-inflammatory substance (mycophenolate mofetil, MMF), an anti-fibrotic substance (enalapril, ENA) and a combination of both substances. In the model of anti-Thy1-induced chronic glomerulosclerosis (cGS) uni-nephrectomized (NX) Wistar rats received a short-term immunological insult through i.v. injection of an antibody, which leads after a short time to a complement-dependent mesangial cell lysis. After setting this insult the renal damage progressed in a self-perpetuating, auto-progressive manner, without additional extrarenal influences, in contrast to hypertensive or diabetic nephropathies. This model allows to investigate in a unique manner purely intrarenal determined processes, as they are taking place in the progression of chronic renal diseases. Altogether 56 rats were assigned into the following groups: a) 2-N = no cGS/ no NX/ no therapy (n=12); b) 1-N = no cGS/ NX/ no therapy (n=8); c) cGS = cGS/ NX/ no therapy (n=8); d) cGS+MMF = cGS/ NX/ MMF therapy (n=8); e) cGS+ENA = cGS/ NX/ ENA therapy (n=8); f) cGS+MMF+ENA = cGS/ NX/ MMF and ENA therapy (n=8).

After a period of 15 weeks urine and blood was collected and the remained kidneys were removed after perfusion before sacrificing the animals. For assessing renal function clinical parameters of relevancy for kidney function and representative markers for inflammation and fibrosis were determined. Therefore measurements of proteinuria (cGS 149±14 mg/ 24h: cGS+MMF 49±14; cGS+ENA 43±10; cGS+MMF+ENA 72±19), systolic blood pressure (148±8 mmHg: 126±5; 124±6; 123±4), tubulointerstitial matrix accumulation (Matrix Score 2,5±0,3; 0,9±0,3; 1,1±0,3; 1,1±0,2), tubulointerstitial expression of TGF-β1 (189±31 pg/ mL: 91±22; 87±10; 107±21), tubulointerstitial lymphocyte (112±14,4 CD4 pos. cells/ section: 42±18,8; 45±14,7; 39±8,6) and macrophage infiltration (187±23,9 ED1-pos. cells/ section: 74±19,8; 53±16,2; 97±12,0) and levels of plasma creatinin (1,2±0,28 mg/ dL: 0,51±0,05; 0,49±0,02; 0,49±0,03) were determined. Furthermore tubulointerstitial fibronectin and PAI-1 expression on protein and mRNA levels, as well as glomerular matrixprotein accumulation, expression of TGF-β1, fibronectin and PAI-1 on protein and mRNA levels, glomerular lymphocyte (CD4, CD8) and macrophage infiltration, blood parameters, urea and GFR were analysed. The results of these parameters are following the representative results of the elected tubulointerstitial parameters.

The present study reveals, that the component MMF is similar effective in the model of anti-Thy1-induced chronic glomerulosclerosis as the clinically established “golden Standard” enalapril in the treatment of chronic kidney diseases and that a combined therapy could not achieve additional effects in relevant parameters characterizing chronic renal disease. The here used pharmacological intervention is giving direct and indirect hints, that tubulointerstitial cellular infiltration and matrix accumulation are directed by using identical or at least very similar pathways in the progression of chronic kidney insufficiency

The results of the present work are contrasting to other experimental studies performed in animal models, which achieved additional additive effects by using a combined anti-inflammatory, anti-fibrotic approach. This might be based on the fact, that divergent animal models (hypertensive nephropathy; cyclosporin-induced nephropathy) and relatively lower dosage of the substances were used. Nevertheless the results are comparable to a recently published study. Here a cohort of randomized patients with IgA-nephropathy pretreated with ACE-inhibitors received MMF in the follow up treatment. Consisting with the findings of this work patients revealed no signs of additional effects in the combined therapy compared to mono-therapy.

Hence this work is an important contribution focussing at therapeutic strategies aiming at human chronic-progressive renal disease. The data of the animal experimental studies are proposing, that a combined therapy consisting of the primarily anti-inflammatory substance MMF and the primarily anti-inflammatory substance ENA provides no additional nephroprotective effects compared to the effects of administering mono-therapies solely.

Summarizing the results of the work it can be proposed, that the pharmacological intervention targeted on influencing tissue inflammation and fibrosis represent similar or at least very closely interacting pathways mediating progression of chronic renal disease and that there is no benefit in treating patients in terms of chronic kidney disease with a dual therapeutic approach consisting of mycophenolate mofetil and enalapril.