ELSEVIER

Effect of Mycophenolate Mofetil on the In Vivo Infiltration of Lymphocytes in the Rat Remnant Kidney

V. Müller, P. Hamar, A. Szabo, E. Knust, M. Vogelsang, and U. Heemann

THE DEVELOPMENT of progressive glomerulosclerosis in hyperfiltrating kidneys has been ascribed to a number of humoral and hemodynamic factors, including the upregulation of adhesion molecules and subsequent infiltration of leukocytes into the damaged tissue. Mycophenolate mofetil (MMF) is a new immunosuppressant that selectively inhibits the proliferation of lymphocytes and additionally downregulates the expression of adhesion molecules in vitro.[1] In this study, we investigated the influence of a short-term pretreatment with MMF on the in vivo migration pattern of lymphocytes in a rat model of hyperfiltration.

METHODS

In 24 Wistar–Furth rats, the right kidney was removed and the left kidney cut to one third of its original size. Urinary protein excretion was monitored monthly.

Sixteen weeks after 5/6 nephrectomy, rats were randomly divided into three groups, and treated for 3 consecutive days with either MMF (20 mg/kg per day), FK 506 (0.16 mg/kg per day), or vehicle. Age-matched naive rats served as additional controls. ^{111}Indium-oxine-labeled lymphocytes (3×10^7 cells/rat) obtained from naive rats were injected intra-arterially, and organs were harvested 8 hours later. The radioactivity of organs was expressed as percentage of injected radioactivity per gram of tissue.

Additionally, the infiltration of lymphocytes (OX19) and monocytes/macrophages (ED-1), as well as the expression of ICAM-1 (CD54) and VCAM-1 (CD106) in the kidneys were determined by immunohistology.

RESULTS

Sixteen weeks after 5/6 nephrectomy, significant proteinuria had developed in all animals as compared with naive controls (116 ± 17 mg/d vs 22 ± 8 mg/d). An increased number of labeled lymphocytes migrated into the remnant kidney as compared with naive controls (0.59 ± 0.14% vs 0.55 ± 0.07%). There was a tendency toward a decreased accumulation of renal lymphocytes following MMF pretreatment (0.56 ± 0.12%), whereas FK 506 had no apparent effect on the process (0.59 ± 0.12%).

Immunohistologic analysis of the kidneys confirmed the patterns of lymphocyte infiltration as determined by radioactivity. Increased numbers of lymphocytes (19.0 ± 1.6 vs 11.3 ± 1.4 cells/FV) and monocytes/macrophages (14.0 ± 1.6 vs 7.4 ± 1.4 cells/FV) were present in the remnant kidneys as compared with naive animals. Whereas the total amount of infiltrating leukocytes did not differ between the 5/6 nephrectomized groups, MMF pretreatment changed the distribution of infiltrating cells; perivascular and periglomerular infiltration of leukocytes was significantly decreased as compared with FK 506 or vehicle animals. Additionally, in 5/6 nephrectomized kidneys, ICAM-1 and VCAM-1 expression was increased as compared with the minimal level observed in naive controls. MMF pretreatment significantly decreased the expression of ICAM-1 as compared with the FK 506 or vehicle groups, but had no effect on VCAM-1 expression.

DISCUSSION

Leukocytes are known to cause kidney damage. They can induce glomerular dysfunction, stimulate the inflammatory response, and determine the extent of glomerular injury.[2] Hyperfiltration, induced by 5/6 nephrectomy, activates the vascular endothium, stimulates expression of several adhesion molecules, and consequently promotes leukocyte infiltration into the tissue.[3] Accordingly, the reduction of functioning renal mass resulted in a decline in kidney function and was associated with an increased infiltration of mononuclear cells in our experiment. Our data suggest that even short-term MMF treatment reduces the expression of ICAM-1, and subsequently decreases the immigration of lymphocytes into the remnant kidney of the rat.

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From the Departments of Nephrology (V.M., P.H., A.S., M.V., U.H.)and Nuclearmedicine (E.K.), University Hospital, Essen, Germany.

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Address reprint requests to Uwe Heemann, Universitätsklinikum Essen, NTP-Ambulanz, Hufelandstr 55, 45122 Essen, Germany.

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