New Aspects of the Treatment of Nephrotic Syndrome

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Abstract. The nephrotic syndrome, caused by glomerulonephritis, diabetes mellitus, or amyloidosis, is still a therapeutic challenge. Newer therapeutic approaches may be sought in the fields of immunosuppression, nonspecific supportive measures, heparinoid administration, and removal of a supposed glomerular basement membrane toxic factor. In immunosuppression, the newer drugs now used in organ transplantation (cyclosporine, tacrolimus, and mycophenolate mofetil) can also be used in the treatment of glomerulonephritis. In nonspecific supportive treatment, angiotensin II receptor antagonists are now used in addition to angiotensin-converting enzyme inhibitors. Positive effects of hydroxymethylglutaryl coenzyme A reductase inhibitors on the nephrotic syndrome have not yet been proven. Cyclooxygenase II inhibitors must be tested but probably have too many renal side effects, similar to those of nonsteroidal anti-inflammatory drugs. Heparinoids or glycosaminoglycans serve as polyanions and thus have protective effects on the negative charge of the glomerular basement membrane. They can now be administered as oral medications. The removal of a supposed glomerular basement membrane toxic factor that induces proteinuria has been attempted for 20 yr and now is usually performed using immunoadsorption. Especially in cases of recurrent nephrotic syndrome after renal transplantation for patients with glomerulonephritis, this approach has been successful in decreasing proteinuria, although in most cases its effect is not lasting but must be continuously renewed.

The nephrotic syndrome with heavy proteinuria is the most severe disease encountered in nephrology, whether the cause is glomerulonephritis, diabetes mellitus, or amyloidosis. In severe cases, patients are grateful when they have reached end-stage renal disease, which usually means the cessation of kidney function and an end to their loss of protein. In some cases, this cannot be achieved with any methods other than renal ablation, e.g., embolization of the kidneys.

The protein barrier of the glomerular basement membrane is charge-selective for smaller proteins and size-selective for larger proteins (1–3). The first stage of fluid accumulation before hypoproteinemia is sodium retention by the distal tubules, perhaps mediated by an abnormal response to atrial natriuretic hormone (4,5). The consequences of severe proteinuria are excessive tubular reabsorption of protein, disturbances of intracellular tubular signaling (with release of vasoactive and inflammatory substances into the interstitium), interstitial inflammatory reactions, and finally renal insufficiency (6).

Many attempts have been made to reverse or influence protein passage through the glomerular basement membrane, especially in cases in which causal therapy of the underlying disease has proved impossible, such as some cases of glomerulonephritis and cases of diabetes mellitus or amyloidosis. New aspects of the treatment of the nephrotic syndrome represent the subject of this article.

Immunosuppressive Drugs

The first controlled trial of immunosuppressive treatment in adult patients with glomerulonephritis and the nephrotic syndrome was undertaken in 1970 with prednisone. That trial confirmed that some kinds of glomerulonephritis responded to immunosuppressive therapy better than others and that patients with the reversal of proteinuria usually did not develop renal insufficiency (7). Consequently, other immunosuppressive drugs, such as azathioprine, cyclophosphamide, and chlorambucil, were tested for the treatment of glomerulonephritis; they improved and stabilized the outcome of treatment, especially for the poorly responding forms of glomerulonephritis [such as focal segmental glomerular sclerosis (FSGS) and membranous glomerulonephritis] (8–10). In recent years, immunosuppressive drugs used for organ transplantation have been increasingly tested for the treatment of resistant cases of glomerulonephritis.

Cyclosporine acts by inhibiting interleukin-2 production and has been used in transplantation since 1980. It has been tested in the treatment of glomerulonephritis since 1986 (11). However, only in 1999 was a controlled trial performed with patients with steroid-resistant FSGS (n = 49); that trial demonstrated that significantly more patients treated with cyclosporine experienced partial or complete remission, compared with patients not treated (12). Controlled trials are difficult to perform for membranous nephropathy, because of the variable spontaneous course of the disease (13). However, a significant reduction in proteinuria was observed for cyclosporine-treated patients with membranous nephropathy (14,15). The mechanism of action of cyclosporine in the treatment of glomerulonephritis is not known. Side effects of treatment are hypertension and nephropathy (16).

Tacrolimus also blocks the activation of the interleukin-2...
gene in T cells. It has been used in transplantation since 1990 and has also been used for the treatment of glomerulonephritis in some treatment-resistant cases (17). No controlled studies exist. As for cyclosporine, the mechanism of action on proteinuria is not known. However, in one case of membranoproliferative glomerulonephritis that was treated successfully with cyclosporine, a treatment switch to tacrolimus (performed because of cyclosporine side effects) caused a relapse of proteinuria, whereas cyclosporine subsequently induced remission (18). Therefore, there must be a difference in the actions of these two drugs.

Mycophenolate mofetil has been used in transplantation since 1993 (19). It suppresses de novo purine synthesis, thus inhibiting T and B cell proliferation as well as the proliferation of smooth muscle cells and fibroblasts; perhaps it is through this mechanism that the drug protects the kidney from progressive disease. Mycophenolate mofetil is used in the treatment of glomerulonephritis in resistant cases such as cases of IgA nephropathy (20). No controlled studies have been performed. The cases presented in the literature primarily involved patients who had been heavily pretreated with other drugs, but those findings indicated at least partial remission in 47 of 63 cases (75%) (20–26).

Nonspecific Supportive Treatment

Angiotensin-converting enzyme (ACE) inhibitors are known to decrease proteinuria by reducing GFR and thus influencing mesangial processes as well as the sieving coefficient and size selectivity of the glomerular basement membrane (27,28). Angiotensin II receptor antagonists have the same effects on proteinuria and are as effective as ACE inhibitors (28,29). The possibility of additive effects of the two types of compounds has not yet been tested.

Hydroxymethylglutaryl coenzyme A reductase inhibitors have strong lipid-lowering effects. It has been suggested that dyslipoproteinemia caused by renal disease, and especially by the nephrotic syndrome, may contribute not only to the accelerated development of atherosclerosis but also to the progression of renal disease (30). In addition to their lipid-lowering effects, statins improve endothelial function and alter the local fibrinolytic balance within the vessel wall, in a way that tends to increase fibrinolytic activity (31,32). However, the lipid-lowering effects of hydroxymethylglutaryl coenzyme A reductase inhibitors with respect to the extent of proteinuria in cases of nephrotic syndrome have not been proven (33).

Nonsteroidal anti-inflammatory drugs have been shown to reduce proteinuria by reducing the GFR (34). The multiple renal side effects caused by prostaglandin inhibition, such as hemodynamic effects on renal perfusion, edema formation, hyperkalemia, and renal toxicity, have led to the restricted use of these drugs. Selective cyclooxygenase II inhibitors have been shown to have the same beneficial effects on proteinuria in rats, with fewer side effects, when administered in low doses; at high doses, cyclooxygenase II selectivity is lost and more of the typical aforementioned side effects of nonsteroidal anti-inflammatory drugs may be observed (35). However, no studies have been performed with human subjects.

Heparinoids

Heparin treatment in glomerulonephritis was shown to lower proteinuria and ameliorate renal insufficiency, in the short and long term, as early as 30 yr ago; these findings were ascribed to the anticoagulant effect of heparin (36,37). However, in an experimental study using rats, it was shown that glycosaminoglycans, which are part of the glomerular basement membrane as well as of heparin, act as polyanions and antagonize the damaging effects of polycations such as protamine, reestablishing the negative charge of the glomerular basement membrane and the podocyte architecture (38). In addition, mesangial cell turnover is decreased (39–41). Especially in cases of diabetes mellitus characterized by disturbances of extracellular matrix degradation, glycosaminoglycans modulate the consequences of these defects on the glomeruli and the retina by inhibiting the overactive transforming growth factor-β cascade (42). When sulfated glycosaminoglycans were administered to human subjects for 1 mo, the effect on proteinuria was small but statistically significant (43).

Glycosaminoglycans are now available as nonanticoagulant oral medications. Pentosan polysulfate is a sulfated oligosaccharide of plant origin with some of the nonanticoagulant features of unfractionated heparin (40). Controlled long-term studies with nephrotic patients with glomerulonephritis or diabetes mellitus are awaited. To date, it has seemed justified to treat severely nephrotic patients with low-mol wt heparin instead of phenprocoumon to establish anticoagulation (which is necessary for these patients, in their hypercoagulable state), as well as to achieve possible beneficial effects on proteinuria.

Removal of a Glomerular Basement Membrane Toxic Factor

The discussion regarding a proteinuric factor in glomerulonephritis, and especially in FSGS, has been underway since the observation of the early recurrence of heavy proteinuria after renal transplantation in a patient with FSGS (44). This suspicion was confirmed by the report of fetal transmission of proteinuria to two children of a mother with heavy proteinuria attributable to FSGS (45). The reduction of posttransplantation proteinuria attributable to recurrent mesangiproliferative glomerulonephritis by plasma exchange was first reported by Solomon et al. (46). The fact that immunoadsorption was more effective than plasma exchange (83% versus 64% mean reduction of proteinuria) in cases involving nephrotic syndrome attributable to glomerulonephritis was reported by Dantal et al. (47,48). Some patients experience complete or partial remission of the nephrotic syndrome after a certain period of plasma removal, but most patients experience relapse 3 to 10 d after the cessation of therapy. Chronic intermittent immunoadsorption must be considered for these patients and seems to be possible for at least months (J. Dantal, personal communication, June 2000). Interestingly, low-density lipid apheresis is also able to decrease proteinuria, in a manner similar to that of immunoadsorption (49,50). Whether this method could be successfully used for patients with nephrotic syndrome attributable to causes other than glomerulonephritis, e.g., diabetes mellitus or amyloidosis, remains to be investigated (51).
It is not yet possible to identify the proteinuric factor. Koyama et al. (52) obtained T cell hybridomas from T cells from a patient with minimal-change nephropathy, which produced a glomerular permeability factor that induced proteinuria and partial fusion of glomerular epithelial cells in rats. Those authors speculated that the factor was a lymphokine. Savin et al. (53) identified such a circulating factor in patients with recurrent nephrotic syndrome after renal transplantation. In rats, this factor was assumed to be tumor necrosis factor-α (54).

Conclusions
For patients with nephrotic syndrome attributable to treatment-resistant glomerulonephritis, some benefits may be obtained with the new immunosuppressive drugs used in organ transplantation, such as cyclosporine, mycophenolate mofetil, and in some cases tacrolimus. For patients with diabetes mellitus or amyloidosis and for some patients with glomerulonephritis that does not respond to any immunosuppressive treatment, no causal treatment is currently possible. As a nonspecific supportive treatment, angiotensin II receptor antagonists are as efficacious as ACE inhibitors. The anticoagulation treatment required for the nephrotic syndrome should perhaps be performed with low-mol wt heparin instead of phenprocoumarin, because of the superior antiproteinuric effects and protective effects on the glomerular basement membrane exhibited by heparin. Alternatively, in addition to their other medications, these patients should receive the oral anticoagulant heparan sulfate. For patients with treatment-resistant FSGS in native kidneys or in renal transplants or for patients with severe nephrotic syndrome attributable to other glomerulonephritides, the removal of a proteinuric factor, via plasmapheresis or immunoadsorption, could be attempted. If this removal is effective but does not lead to persistent remission, chronic intermittent immunoadsorption should be considered. Even today, renal ablation (by embolization or surgical removal of the kidneys) and subsequent chronic dialysis treatment may be the only feasible way to protect patients from the consequences of severe proteinuria (55,56).

References


