LEADING ARTICLE

RETARDING THE PROGRESSION OF CHRONIC RENAL FAILURE: IS IT POSSIBLE?

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Nowadays, there are certain measures which can be instituted in an attempt to retard the progression of chronic renal failure (CRF) to end stage renal failure (ESRF). Some of these measures can be applied to any patient with kidney disease, viz, control of systemic hypertension, protein restriction and reduction of intraglomerular hypertension.

In any patient with kidney disease, if systemic hypertension is uncontrolled, the patient runs the risk of developing accelerated progression to ESRF, sometimes within a matter of months, especially when the uncontrolled hypertension undergoes an accelerated phase and behaves like malignant hypertension. In our study[1] of IgA nephritis, in patients with renal impairment, those with well controlled hypertension developed ESRF three years later compared to those with uncontrolled hypertension. These three years represent big savings in terms of expenses for renal replacement therapy.

Protein restriction is routinely instituted in all patients with renal impairment in an attempt to reduce the renal damage resulting from hyperfiltration. In any kidney where some glomeruli have been damaged or sclerosed, the remaining glomeruli will undergo hyperperfusion or hyperfiltration. This is associated with intraglomerular hypertension because of increased blood flow at the afferent arteriole of the glomerulus and angiotensin II mediated vasoconstriction at the efferent arteriole. The result is an increase in single nephron glomerular filtration rate with proteinuria. However, with time the affected glomerulus will undergo scarring or glomerulosclerosis. Dietary protein restriction will decrease the amount of macromolecules entering the perfused glomerulus resulting in less blood flow and reduction of intraglomerular blood pressure. In patients with diabetic nephropathy, when euglycemia is achieved, there is also less hyperperfusion since less macromolecules will be entering the glomerulus. This will help to reduce intraglomerular hypertension. Another way to reduce intraglomerular hypertension is to treat patients with angiotensin converting enzyme (ACE) inhibitors. These agents will decrease the vasoconstriction at the efferent glomerular arteriole and restore normotension within the glomerulus.

Recently[2], it has been shown that abnormality of lipid metabolism may play a central role in the progression of initial glomerular injury to glomerular sclerosis. Diet induced hypercholesterolaemia may be the initiating factor for endothelial injury, especially low density lipoprotein (LDL) and very low density lipoprotein (VLDL) cholesterol. Lipoproteins can pass through the damaged glomerular filter into the mesangium, thereby enhancing the flux of macromolecules and giving rise to hyperperfusion injury.

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Coagulation and thrombosis also cause significant renal injury. In the glomerular circulation, glomerular capillary hypertension is capable of damaging the endothelium. This can activate platelets and result in glomerular thrombosis[2]. Thromboxane A2 (TXA2), primarily formed by platelets, is a powerful vasoconstrictor and platelet aggregator. On the other hand, prostacycline (PGI2), synthesized from arachidonic acid by the endothelium, is an extremely potent vasodilator as well as inhibitor of platelet aggregation. Interference of PGI2 by TXA2 can inhibit platelet activity. Purkerson[3] utilised a selective oral inhibitor of TXA2 synthesis (OXY 1581) and demonstrated decreased total urinary protein and TXA2 excretion, decreased blood pressure and improvement in the renal histology and increase in single nephron glomerular filtration rate (SNGFR). Platelet aggregation leads to intraglomerular thrombosis and plays a key role in the development of glomerulosclerosis.

It has also been shown that administration of coumadin at doses which caused significant prolongation of prothrombin time and bleeding time, inhibits development of progressive hypertension and uraemia in rats with experimental partial infarction[4]. Non-anticoagulant heparin compounds and whole heparin in a dose not sufficient to prolong activated partial thromboplastin time (PTT) both ameliorated functional and histologic abnormalities in chronic aminonucleoside nephrosis. The beneficial effects of heparin may be through an anti-proliferative effect on glomerular mesangial cell[5].

In patients with diabetic nephropathy with renal impairment, it is important to control hypertension and restrict dietary protein intake to 40 grams a day. ACE inhibitors could be employed in those with severe proteinuria, presumably resulting from hyperperfused glomeruli.

Patients with vesico-ureteric reflux with renal impairment should have urinary tract infection aggressively treated and then put on prophylactic antibiotics for three years from the date of the last episode of urinary tract infection. In addition, hypotensive therapy and protein restriction should be instituted.

In patients with renal stones, one should be vigilant in detecting and treating urinary infections and obstructive uropathy if renal function is to be preserved.

For those with polycystic kidneys it is important to control hypertension, treat urinary tract infections when necessary and remove stones to prevent renal damage due to obstructive uropathy.

All patients with hypertension should ensure that their blood pressure is checked regularly and that they are compliant with the treatment as severe uncontrolled or accelerated hypertension behaves like malignant hypertension, and the patient runs a high risk of developing ESRF.

Reversible causes of renal failure could be identified and removed or treated. These are multiple myeloma, obstructive uropathy, malignant hypertension, hypokalaemia and hypercalcemia as well as offending chemical agents like hydrocarbons and those posing as occupational hazards like lead and mercury.

Acute reversible elements causing acute on chronic renal failure should also be identified and treated if renal function is to be preserved in patients with pre-existing renal disease and renal impairment. These are dehydration, sepsis, uncontrolled hypertension, obstruction and nephrotoxic agents.

Pregnancy in any patient with renal disease is always cause for concern. This is especially so in a patient already with mild renal impairment or a renal biopsy showing more than 25% glomerulosclerosis. In general, patients with renal disease should avoid pregnancy if there is renal impairment or if hypertension proves difficult to control as these two factors in pregnancy often cause high foetal mortality and maternal morbidity, in particular the danger of causing an accelerated and acute deterioration to ESRF in a patient who already has mild renal impairment at the beginning of pregnancy.

Patients with lupus nephritis should avoid pregnancy if the disease is still active as there is a 50% to 60% incidence of exacerbations compared to those with inactive disease. Foetal survival is only 50% to 75% for those with active compared to those with inactive lupus nephritis where there is 90% foetal survival. Pregnancy induces an additional 10% glomerular scarring in patients with underlying glomerulosclerosis as pregnancy is associated with glomerular hyperperfusion and a low grade disseminated intravascular coagulation (DIC).

Cytotoxic drugs have been shown to modify the diseases due to systemic necrotising arteritis, systemic vasculitis, Wegener's granulomatosis (prednisolone, cyclophosphamide). Prednisolone have been used to treat lupus nephritis with preservation of renal function[6]. A combination of either cyclophosphamide or azathioprine with prednisolone has demonstrated benefit of better preservation of renal function as compared with prednisolone alone. Numerous reports based largely on uncontrolled trials or inadequately controlled trials attest to the efficacy of specific pharmacologic agents in the treatment of many types of glomerular disorders; these include daily and pulse therapy, cytotoxic drugs, anticoagulants and antiplatelet drugs in crescenteric glomerulonephritis[7-9].

In Singapore, we have conducted several controlled therapeutic trials in patients with IgA nephritis in an attempt to retard the progression of these patients to ESRF. Our earlier trial[7] using a combination regimen of cyclophosphamide, dipyridamole and low or anti-thrombotic dose of warfarin (Triple Therapy) showed that patients in the treatment group had less deterioration of renal function compared to those in the controlled group. Among the patients in the treatment group (n=27) there was no significant difference in the serum creatinine levels, creatinine clearance and serum albumin before and after the 3 year prospective controlled trial but proteinuria decreased significantly (from 2.4 ± 2.5 gm/day to 1.0 ± 0.9 gm/day, $p<0.01$). In contrast, in the controlled group (n=21), creatinine clearance decreased from a mean of 109 ± 23 mls/min to 79±27 mls/min ($p<0.01$) and serum creatinine rose from a mean of 1.1 ± 0.2 mg/dl to 1.7 ± 1.9 mg/dl ($p<0.02$). There was no change in the degree of proteinuria or the level of serum albumin. Repeat renal biopsies after the trial revealed less progression of glomerulosclerosis in the treatment group[8].

Subsequently, in another controlled trial[9] using only dipyridamole and low dose warfarin in patients with IgA nephritis with renal impairment, we demonstrated that patients in the treatment group had less significant deterioration of renal function compared to the control group. In the treatment group, the 11 patients showed no significant differences in the serum creatinine levels or creatinine clearance at entry and at the time of last follow up. However, there was a significant decrease in proteinuria (from 1.36 ± 1.20 gm/day to 0.58 ± 0.28 gm/day, $p<0.05$). In the control group (n=9) serum creatinine increased from a mean of 2.10 ± 0.45 mg/dl to 2.97 ± 0.84 mg/dl, $p<0.01$. Creatinine clearance decreased from 50 ± 28 ml/min to 39 ± 22 ml/min but this difference was not significant. There was no change in the degree of proteinuria. Patients in the control group had been in the trial for a period of 12.6 ± 5.3 months, but this was not significantly different from that of treatment group (10.5 ± 5.7 months). This trial also showed that the use of cyclophosphamide was no longer justified.

In another study based on a 5 year follow up of patients who were on the original Triple Therapy[10], we showed that 6 out of 13 patients in the control group developed ESRF whereas none of the 13 patients still on dipyridamole and low dose warfarin have reached ESRF yet. In IgA nephritis there is evidence for platelet aggregation and a thrombogenic tendency in glomeruli subjected to raised intraglomerular blood pressure[11]. It is our surmise that dipyridamole and low dose warfarin may be useful in this respect[11].

However, the task of discussing prevention of glomerular damage with pharmacologic agents is severely limited by available data. More prospective well controlled clinical trials are urgently needed.

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