EVALUATION OF IMMUNOSUPPRESSIVE THERAPY IN CASES OF STEROID RESISTANT IDIOPATHIC GLOMERULONEPHRITIS

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Abstract: *The present prospective randomized study was carried out on 30 adult cases of steroid resistant idiopathic membranous (MGN) or membrano proliferative glomerulonephritis (MPGN) and the effects of immunosuppressive therapy were evaluated. Thirty (30) patients with progressive deterioration of renal functions were included which were divided in to two groups. After baseline investigations and pre-informed written consent, 20 cases of group A were given azathioprine (1-2 mg/kg / body weight) and prednisolone (0.5 mg/kg/body weight) for a minimum period of 6 months and the renal functions were evaluated at monthly intervals, Group B cases (10 patients) served as controls. After six months of immunosuppressive therapy, creatinine clearance increased in group A, where as it decreased slightly in group B and the differences were statistically significant (P<0.001). The proteinuria decreased significantly in group A patients (P<0.01) where as in Group B it increased (P>0.05). Cholesterol did not change significantly in the two groups. All the patients tolerated the drug well. In group A, 20% patients had complete remission and rest 80% had partial remission, where as in group B, 40% patients had stablilzation of renal functions, 40% had no change and 20% deteriorated. Hypertension and persistent proteinuria were associated with poor4 prognosis.*

Conclusions: It is therefore, concluded that immunosuppressive therapy induced remission in a significant number of patients. However, a large study is needed to confirm the long term survival in such patients.

INTRODUCTION

Chronic glomerulonephritis is leading cause of chronic renal failure. The primary mechanisms, involved in pathogenesis of idiopathic glomerulonephritis are largely antibody mediated. 1 However, there is considerable evidence that cell medicated immune reactions are also involved. High rates of remissions have been observed with steroid and cytotoxic drugs and combination of azathioprine and prednisolone has been reported to beneficial in idiopathic membranous nephropathy specially with deteriorating renal functions. 3-5 However, a few studies have not found the use of azathiprine to be beneficial. 6-8. Therefore, the treatment of steroid resistant idiopathic glomerulonephritis is not only frustrating but is also controversial. It was in this context that the present study was planned to evaluate the effects of this immunosuppressive therapy in case of steroid resistant idiopathic glomerulonephritis.

MATERIAL & METHODS

The study was carried out in 30 adult cases of steroid resistant idiopathic glomerulonephritis (SRIGN). Only cases with MGHN and MPGN with deteriorating renal functyions with glomerular filtration rate (GFR)< 80.0-ml/min and serum creatinine >2/5 mg% were included in this study. Patients with secondary gloerulonephritis were excluded. The diagnosis of SRIGN was based on histopathological examination and relevant investigations. The patients group consisted of two groups. Group A cases were given a combination of azathioprine (1-2 mg/kgbody weight) and prednisolone (0.5 mg/kg/body weight) for a minimum period of 6 months and the renal functions were evaluated at monthly intervals. Group B cases (10 patients) served as control and it included only those cases of glomerulonephritis who dropped out of the study or refused for their inclusion. Remission was defined as complete when renal functions returned to normal (serum creatinine decreased to < 1.5 mg%) and proteinuria decreased to non nephritic range. Partial remission was defined when there was an improvement in the renal function but proteinuia persisted <3.5 gm/ day. No response was indicated by non change in renal functions or an increase in the serum creatinine by less than 50% of the basal value. Deterioration of renal functions was indicated by a further rise in serum creatinine levels more than 50% of base line value.

RESULTS

The mean age of the patients was 33.4±13.4 years. There were 18 males and 12 females. In group A, there were 14 cases of MPGN and 6 of MGN where as in group B, eight cases were of MPGN and 2 cases of MG. The basal biochemical parameters including age, the degree of renal failure, proteinuria etc., were alike in the two groups (Table-1)

Table-1: *Showing Baseline Renal Profile in the two groups*

Renal Parameter	Group A	Group B	P value
Blood Urea (mg %)	128.5 ±34.7	132.5 ±19.4	>0.05
Serum Creatinine (mg%)	4.3± 0.9	3.97± 0.48	>0.05
GFR (ml/min)	19.9 ±8.9	30.05 ±2.39	>0.05
Proteinuria (g/day)	4.4± 1.6	2.47± 0.5	>0.05
Serum Chlestol (mg%)	280.5± 96.0	264.2± 74.2	>0.05
Serum Uric Acid (mg%)	6.1 ±1.5	5.7 ±1.2	>0.05
Serum Protein (gm%)	5.8± 1.4	5.9± 1.2	>0.05
Serum Calcium (mg%)	8.4± 0.5	8.2± 0.4	>0.05
Serum Phosphate (mg%)	4.9± 0.6	4.8± 0.5	>0.05

Table 2: *Renal Functions Following Immunosuppressive Therapy*

Parameter	Group A before therapy	Group B After therapy	P paired
Blood Urea (mg %)	128.5 ±34.7	64.0 ±20.1	<0.001
Serum Creatinine (mg%)	4.3± 0.9	1.8± 0.6	<0.01
GFR (ml/min)	19.9 ±8.9	52.0 ±22.5	<0.001
Proteinuria (g/day)	4.4± 1.6	2.5± 1.6	<0.01
Serum Chlestol (mg%)	280.5± 96.0	236.5± 59.5	<0.05
Serum Calcium (mg%)	8.4± 0.5	9.01± 0.62	>0.05

Following immunosuppressive therapy there was a significant rise in GFR and fall in serum creatinine, blood urea, serum cholesterol and proteinuria (Table-2) in group A patients as compared to group B. 20% patients achieved complete remission and rest 80% were in partial remission following six months therapy, where as in Group B 40% patients had stabilization of renal functions, 20% deteriorated and 40% had no change. Therefore, percentage of patients going in to remission (complete + partial) was significantly higher in Group A as compared to group B. Further an attempt was made to find out the factors associated with poor outcome. The patients who had complete remission had significantly lower systolic blood pressure, as well as base line biochemical parameters like blood urea, serum creatinine and cholesterol as compared to those

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Table-3: *Baselines Characteristics of patients who went into remission (complete / partial) after immunosuppressive therapy*

Parameter	Complete remission	Partial remission	P value
Age (years)	31.0±12.5	32.8±13.3	>0.05
Sex (Male: Female)	1:1	1:3:1	>0.05
Duration (months)	33.0±11.5	28.2±22.4	>0.05
Systolic Blood Pressure (m Hg)	125.0±12.9	148.0±15.5	<0.05
Anemia	None	9	-
Oliguria (< 400 ml / d)	1	8	<0.01
Blood Urea (mg %)	117 ±12.9	127.3 ±35.5	>0.05
Serum Creatinine (mg%)	3.8± 0.3	4.4± 1.1	>0.05
Serum Chlestol (mg%)	231.8± 59.3	298.3±107.1	>0.05
Serum Calcium (mg%)	8.2±1.05	8.1±0.73	>0.05
Proteinuria (g/day)	4.3± 2.1	4.5± 1.5	>0.05
GFR (ml/min)	19.4± 7.3	19.5± 10.0	>0.05
Kidney size (cm)	9.0± 0.41	8.8±0.36	>0.05

who did not respond (Table-3) Further early amelioration of proteinuria was associated with better prognosis and outcome as compared to those who had late decrease in the urinary excretion of protein. When the type glomerulonephritis was taken in to consideration, it was observed that 25% of MPGN cases had complete remission and 75% had partial remission, where as all the cases of MGN had partial remission and none of the cases had complete remission. However, no histopathological markers of bad prognosis could be identified. Fixed drug reaction, hematemais and activation of pulmonary tuberculosis were seen in one case each in Group a and none in Group B.

DISCUSSION

In MPGN, the lesion is due to glomerular localization of preformed circulating immune complexes, where as in MGN, the lesion is due to a reaction of circulating antibodies with intrinsic glomerular antigen. The appearance of population of large radius pores, leading to increase in fractional IgG clearance : local deposition and activation of complement mediated injury are the major parts of the cascade. Fibrosis and sclerosis leads to further progression of renal disease. Therefore steroid and cytotoxic drugs, which have anti inflammatory action, are though to be effective in halting the progression of renal disease.9 In addition, steroids also effects the renal hemodynamics leading to increase in GFR. The fall in proteinuria is though to be due to the direct action of corticosteroids on glomerular basement membrane. 10. An alternative hypotheis is that they have anti interleukin action and relieve proteinuria by interfering with the cytokine cascade.11

Immunosuppressive therapy produces clinical benefits by producing several alterations in the immune system of the body. These included the inhibition of helper, inducers and cytotoxic T lymphocytes. They also influence the cell released mediators of inflammation and fibrogenesis 12. Azathioprine, is chiefly use in patients who are resistant to steroid and have frequent elapses following withdrawal of steroids. The action of this drug is at different level than steroid therefore, addition of azathioprine result in optimization of therapeutic response with minimum iatrogenic mortality and morbidity. There are a few studies available where the combination of azathioprine and prednisolone have been found to be beneficial in SRIGN, especially in MGN. 3-5,13. However, there are conflicting reports as well where the combination was not found to be beneficial in SRIGN,3,7. Therefore the literature on the subject is not only scant but is also controversial hence this study. 5 In the present study all patients tolerated the drug well. In group A, 20% patients had complete remission and rest 80% had partial remission, where as in Group B, 40% patients had stabilization of renal functions, 40% had no change and 20% deteriorated. Hypertension and persistent proteinuria were associated with poor prognosis. Two of the previous studies, 6-7 which did not find any beneficial effects were not well planned and were retrospective; hence their results can not be compared. The number of the patients in Barker study 5 were only 4 where as Brown et al4 reported similar observation as reported by us. On the other hand the recent 10 year follow up study 8 reported no beneficial effects.

However, in this study also they did not analyze the bad prognostic factors which might be operating in their patients. A number of factors like advancing Age 14, long duration of disease 17, presence of systolic or diastolic hypertension 16, heavy proteinuria 17, higher basal value of serum creatinine and urea 18, late amelioration of proteinuria and presence of certain histopathological markers like crescents and tubulointerstitial inflammation etc. are known to be associated with poor outcome, 19-20 Hypertension accelerates glomerular injury through hemodynamic mechanism, greater degree of proteinuria, extra capillaryproliferation and glomerulosclerosis. Further its presence may denote fluid over load or actually advanced renal disease. In addition, hypercoagulability and hyperlipidemia may also independently lead to progression of renal disease. Hyperlipidemia through complex mechanisms of macrophage infilitration and interstitial cell proliferation, contributes to the progression of glomeruloscelerosis In the present study, only bad prognostic factor was the presence of significantly elevated systolic blood pressure in the non responders. Although a number of histopathological markers have been described to be associated with poor out come. However, except for the type of glomerulpathy, no pathological marker could be identified in the present study. The presence of crescents and a large number of crescents and a large number of non functioning (sclerosed) glomeruli, may in fact denote a serve renal pathology rather than a prognostic market. Although the number of patients included in the present study were small and the duration of the study and follow up were 6 months and a year. However, the result of this study no suggest that it is essential that a good work up of the individual case is of utmost importance to predict the long term survival in these cases and every case of SRIGN with deterioriating renal functions deserves immunosuppressive therapy.

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