Editorial

Current Treatment of Glomerulonephritis

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Although the entity of glomerulonephritis (GN) has been well recognised for over 300 years, effective modalities of treatment are far from satisfactory. These are various reasons for this, these include a) controversies in the histological classification of glomerulonephritis, b) the multiplication of immune mechanisms c) complexity of clinical presentations and d) the availability of various immune modulating agents for clinical investigation.

The lack of well designed, controlled, randomised, double blind studies is because of the poor prognosis of some of the rapidly progressive nephritidies and the conflict with ethical considerations such planned studies confront.

However the easy availability of kidney biopsy, the better understanding of renal histology and immune mechanisms and the introduction of immunological techniques in histology have to a great extent helped in better treatment protocol and strategy.

Glomerulonephritis can present to the clinician in the following ways.

a) asymptomatic haematuria or protienuria
b) the nephrotic syndrome
c) the acute nephritic syndrome
d) rapidly progressive renal failure or acute renal failure
e) chronic renal failure
f) mixed pictures

It is well recognised that any strategy for specific treatment for glomerulonephritis should and must include treatment according to a histological type.

Renal histology should be done, if specific treatment is envisaged of any one of the clinical presentations listed above, unless there is a strong correlation clinico-pathologically for the presentation which does not require biopsy.

In the childhood nephrotic syndrome which is commonly due to minimal change glomerulonephritis, making that assumption one could proceed with specific treatment without a biopsy. Another example is the Post-streptococcal acute nephritic syndrome where if the clinical presentation is clear cut and the course of the disease is as expected, no renal biopsy would be necessary on the assumption that Acute diffuse endothelial proliferative glomerulonephritis exists and symptomatic measures alone may be instituted as there are no specific measures needed. In all other types of glomerulonephritis a renal biopsy is mandatory to a scientific approach to therapy.

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The histological types which will be considered in turn with respect to treatment would include

Minimal change disease (MCD),

Membranous glomerulonephritis (MN),

Membrano-proliferative glomerulonephritis (MPGN) also called Mesangiocapillary glomerulonephritis,

Crescentic glomerulonephritis other than anti Glomerular Basement Membrane (GBM) disease (CGN),

Anti GBM disease (AGBMN),

Mesangial IgA disease (IgAN),

Focal and Segmental glomerulosclerosis (FSGS)

The management of patients with GN would include general measures such as dietary modifications, diuretics for the control of oedema, antihypertensives for the control of hypertension, measures to control hypoalbuminaemia, and measures to control hyperlipidaemia. These will not be considered further.

Specific measures which include corticosteroid therapy, immunosuppressive therapy (with cyclophospamide, azathioprine, chlorambucil, cyclosporin A), anticoagulant/fibrinolytic agents (eg. dipyridamole, warfarin, aspirin), plasma exchange therapy (plasmapheresis) would form the important areas to highlight in this article.

Secondary form of GN eg. Lupus nephritis and GN occurring in pregnancy or after transplantation are not considered here. The main types of GN and recent approach to therapy is detailed below.

Minimal change glomerulonephritis

The treatment of nephrotic syndrome in children is now well established with the guidelines of the International study of kidney disease in children (ISKDC) of 1978[1]. Most paediatricians all over the world today follow this treatment protocol and this entails the use of prednisolone 10mg 4 times a day for 10 days and reducing 10mg from the dose schedule every 10 days resulting in a 40 day course when a majority (over 85%) would respond and enter a remission phase.

It is now well recognised that the patients with MCD after the first course of the treatment could behave in various ways viz.

Primary responders without relapses / infrequent relapses (less than 2 relapses in the first 6 months) / frequent relapses (more than 2 relapses in the the first 6 months), **Steroid dependent responders, Primary non-responders, Late responders** and the rare **Spontaneous responders.**

It is recommended that at each one of the relapses the same ISKDC regimen is restarted and if the frequency of the relapses is high then cyclophosphamide or azathioprine has been used in addition to the prednisolone[2]. However azathioprine has not been found to be very effective in this situation[3]. Cyclophosphamide has had a long reputation as the drug of choice in this situation[4]. The side effects of testicular atrophy and teratogenic effects known with cyclophosphamide make it necessary that it be restricted to children only with frequently relapsing disease and those with or without steroid dependence having features of severe steroid toxicity and the duration of the treatment should preferably not exceed 4 to 8 weeks[5].

Thus a patient with MCD presenting with nephrotic syndrome has an excellent long term prognosis if he has minimal glomerular changes on light microscopy showing only foot-process fusion and there is absence of immungolobulin on immunofluorescent microscopy or immunohistochemistry and there is usually a complete remission most of the time following the first course of steroids. Even so multiple relapses still occur and frequency of the relapses decreasing after the 10th year of the disease. Lasting remission is known to occur only in 7%[6] and 18%[7] of patients.

The use of cyclosporin in steroid resistant nephrotic syndrome and in those MCDs which have progressed to FSGS has received the attention of many researchers who presented their findings at the International Congress in Nephrology, Tokyo, 1990. The consensus emerged that although cyclosporin A was useful in achieving a remission in some of these difficult patients, they relapsed regularly on withdrawing the drug. It is thus not going to be a lasting panacea for this form of the disease.

Membranous glomerulonephritis

The treatment of MN has been a subject of much controversy[8]. In the early 1980s the Inter Hospital Collaborative Study in the United States — a controlled study of short term treatment in adults with Membranous nephropathy[9] had suggested that a relatively brief 8 week treatment with high dose (125mg prednisolone per 24 hours) every other day was capable of modifying the medium term evolution of renal failure in this condition.

Following up on this Ponticelli has well summarised the present position with regard to the treatment of MN and has popularised the now well accepted treatment protocol for MN called the Ponticelli regimen[10]. This therapy which was set up in Italy using a complex regimen of a 6 month treatment of low dose oral steroids, oral chlorambucil and prednisolone 0.5mg/kg for alternate months and three pulses of intravenous methylprednisolone of 1Gm each daily given at the beginning of the prednisolone months. A clear effect has been seen in the treated patients with impressive medium term and long term protection of idiopathic MN patients from going into renal failure after the cessation of this treatment. The objective of this to achieve the maximum benefit with minimum side effects.

The first reported use of this regimen in Sri Lanka was presented in 1991 at Sri Lanka Medical Association Annual Academic Sessions[11].

Since there are gross differences in the apparent incidence of MN in different parts of the world where MN causes Nephrotic syndrome there does not seem much justification in treating patients who have MN on renal biosy but do not have evidence of Nephrotic Syndrome (protienuria >3.5Gm per 24 hours).

Cyclosporin has also been used in patients with MN by the Canadian collaborative group[12]. The results from this study have not been very impressive and therefore the Ponticelli regimen is clearly the most attractive therapeutic modality available today for the treatment of MN.

Membrano-proliferative Glomerulonephritis

The best treatment for this subgroup remains contentious[13]. West and colleagues have consistently advocated the use of high dose (60mg/24 hours alternate day prednisolone therapy) despite many early reports that it showed no effect. Their uncontrolled reports are impressive[14] Donaldo et al have evaluated the use of aspirin (975mg/24 hours) and dipyridamole (225mg/24 hours) in adults with MPGN[15]. Although there was a significant decrease in the fall of renal function there was interestingly no effect on protienuria. There have no subsequent publications which have commended this therapy and most other authors have thought that the improvement was transient in all patients since most of them went into renal failure within 5 years. However in a GN which has a very bad overall prognosis the postponement of renal failure cannot be looked down upon as all types of treatment available for MPGN today do the same thing and there is no curative therapy for this type of GN. There is a resurging interest in the uncontrolled observations by the Melbourne group on the use of the cocktail of drugs viz. prednisolone, cyclophosphamide, warfarin and dipyridamole.[16]

In our own setting in Sri Lanka I have advocated the use of prednisolone, cyclophosphamide and persantin, as anticoagulation control in rural areas is far from satisfactory when warfarin is added on. We have had a few unfortunate, avoidable large haemotomas due to the poor backup in the periphery. It is much safer not to use warfarin in view of this in patients who may not have the know how and the facility to control anticoagulation available.

Crescentic glomerulonephritis (other than anti-gbm disease)

The use of Methylprednisolone pulse therapy in 1 gm daily doses to a maximum 3–7 gms has been noted by Bolton to recover or retain renal function in most such instances[17]. This type of therapy has largely superseeded the combined anticoagulation and immunosupression therapy which was made popular by Cameron[19]. It would thus be recommended patients with CGN would be best treated with Methylprednisolone pulse therapy followed by oral steroids.

Anti GBM disease

In untreated patients, only 11% of those with AGBMN retain or recover renal function in Glassock's analysis[19]. Patients who are oligo-anuric and who have plasma creatinine over 600 mmol/L do very badly on most treatment regimens.

The rapid removal of anti-GBM antibody using repeated plasma exchange with supporting dialysis covered by antibiotic treatment (as infection with Pseudomonas is known to accelerate immune deposition and destruction) combined with immunosuppresion of which cyclophosphamide is the most essential component has been used to avert or reverse declining renal function in a great majority of patients. In patients who come very late needing urgent dialysis no specific treatment except dialysis is worth considering as the antibody usually disappears within a year or two and does not recur after transplantation. However in patients who may present with troublesome lung haemor-

rhage, there is evidence that plasma exchange can be used to control lung haemorrhage.

IgA Nephropathy

The data coming out of South East Asian studies support the idea that the use of prednisolone may be effective. Since this disease has a slow evolution, a controlled trial of any treatment is going to be more tedious and difficult than in other GNs. Therapeutic agents like prednisolone and cytotoxics are not routinely indicated because of the indolent and unpredictable course. Antithrombotic agents have not been explored adequately. It must be remembered however that a report from the Necker Hospital in Paris stated that chronic renal failure is unpredictable with 25% of those with IgAN ultimately developing renal impairment and of these over 66% developed chronic renal failure.

Non-IgA Mesangial GN with or without proliferative changes although forming a not insignificant proportion of our nephrotics, does not have a clear recommendation for therapy and often is either left alone or treated with steroids if the symptoms are troublesome.

Focal and segmental glomerulosclerosis

The majority of patients with FSGS experience a progressive decline in glomerular filtration rate as well as hypertension and persistent protienuria. There is usually no response to steroid treatment initially and the asymptomatic protienuric becomes nephrotic with time. The development of the nephrotic syndrome adversely affects the prognosis of FSGS. The recurrence rate of FSGS in renal allograft is high and there is a high incidence of preeclampsia and renal impairment in those patients with FSGS who go through pregnancy. If FSGS develops on a background of MCD the patient remains steroid responsive, however if FSGS develops on a background of Mesangial Proliferative GN the prognosis is poorer.

More recent trends expressed by researchers at the International Congress of Nephrology, Tokyo 1990 (personal communication) have focussed on an aggressive approach to treatment with steroids and immunosuppressives. Various reports of methylprednisolone, cyclosprin therapy, immunosuppresive therapy, have all suggested a disease modification with advantages to the patient. Further research is awaited in this particular group which is receiving a lot of attention.

Conclusion

It is thus clear that the treatment of GN in many ways is inefficient and sometimes is completely ineffective. We do not know enough about the cost benefit balance for almost all of the treatments outlined above, including some of proven benefit. How many produce long term rather than temporary remission is again almost unknown. Whether really new methods of treatment such as the use of monoclonal antibodies directed against specific subsets of white cells or lymphokine receptors will prove effective in the future remains uncertain. It will be the complexity and resilience of immune systems which when unravelled in the future, would bring in advances in completely unexpected direction.

Although much attention has been paid to the treatment of the specific factors in reducing morbidity of GN there is greater interest in the general

measures as well. There has been a steady trend in the renal literature towards the earlier introduction (when creatinine clearance is approx. 60 mls/min) of low protein diet (20 Gm protien diet) in progressive renal disease to increase the longevity of such kidneys and in the last International Congress of Nephrology, Tokyo in 1990 (personal communication) there was a clear unfolding of the nephrotoxic role of high serum lipid values and therefore the importance of setting up clinical trials with lipid lowering agents in nephrotics being emphasised.

The treatment of the various types GN which is even more relevant to us in the Third World as we do not have as yet large facilities for dialysis and transplantation and therefore preventive nephrology either primary or secondary in the form of effective therapeutic regimen would definitely be welcome to those with progressive GN.

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