THE NEW OXFORD 'MEST' SCORING SYSTEM IN IgA NEPHROPATHY AND THE EFFECT OF LOW-DOSE STEROID WITH MYCOPHENOLATE MOFETIL (MM) IN THE TREATMENT OF IgA NEPHROPATHY

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ABSTRACT

CONTEXT

Primary IgA nephropathy is characterised by recurrent episodes of gross haematuria concomitant with upper respiratory tract infections or other mucosal inflammatory processes.

AIMS

Assess the histopathological changes in the kidneys after giving MM with low-dose steroids.

SETTINGS AND DESIGN

Mesangial hypercellularity – in < or > 50% glomeruli (M0 or M1); Endocapillary hypercellularity – present (E0)/absent (E1); Segmental sclerosis present (S0)/(S1) absent; Tubular atrophy/interstitial fibrosis – 0-25% (T0), 26-50% (T1), > 50% (T2).

METHODS AND MATERIALS

IgA Nephropathy patients receiving MM with low-dose steroids (Group M) and conventional therapy (Group C), biopsied and scored as per Oxford MEST classification were included. The treatment response was assessed for Mesangial hypercellularity, Endocapillary hypercellularity, Segmental sclerosis/adhesions and Tubular atrophy/interstitial fibrosis.

STATISTICAL ANALYSIS USED

SPSS version 16, Independent sample T test, paired sample T test, one-way ANOVA and McNemar Chi-square tests.

RESULTS

Of the total enrolled 46 subjects, 32 were included in Group M and 14 were included in Group C. In the Group M, mean proteinuria significantly decreased from 1650 mg to 900 mg, mean eGFR increased from 66 mL/min. to 72 mL/min. (p=.001). In the Group C, mean proteinuria decreased significantly from 1300 mg to 1050 mg (p=0.1), mean eGFR decreased from 72 mL/min. to 69 mL/min. (p=0.25).

CONCLUSIONS

Mesangial hypercellularity and endocapillary hypercellularity have direct correlation with proteinuria. Therapy with MM and steroids is effective in retarding the proteinuria, microhaematuria and progression of the disease in IgAN; reversing the mesangial hypercellularity and endocapillary hypercellularity and preventing the progression of segmental sclerosis and tubular atrophy.

KEY MESSAGES

Mesangial hypercellularity and endocapillary hypercellularity have direct correlation with proteinuria. Therapy with MM and steroids is effective in retarding the proteinuria, microhaematuria, progression of the disease in IgAN, reversing the mesangial hypercellularity and endocapillary hypercellularity and preventing the progression of segmental sclerosis and tubular atrophy.

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INTRODUCTION: Primary IgA nephropathy, or Berger's disease, is characterised by recurrent episodes of gross haematuria concomitant with upper respiratory tract infections or other mucosal inflammatory processes. In other patients, microscopic haematuria and/or proteinuria are the only symptoms. Steroids are the mainstay of treatment in patients with proteinuria > 1 g/day.

MM with low-dose steroids have been proposed to reduce the progression of disease and proteinuria. Aim of

the present study is to assess the histopathological changes in the kidneys after giving MM with low-dose steroids.

Subjects and Methods: Validation of the New Oxford MEST scoring system of IgA Nephropathy in our patients and to assess the response to combination of low-dose steroid + MM to reduce proteinuria and to preserve GFR.

Inclusion Criteria:

- Cases are biopsy-proven IgAN.
- Adults more than 15 years.
- Initial eGFR> 30 mL/min. per 1.73 m^2.
- Initial proteinuria>0.5 g per 24 hrs. in,
- All patients with hypertension controlled to <130/85 mm of Hg with antihypertensives.
- All patients received ACE-I/ARB irrespective of their blood pressure status.

Exclusion Criteria:

- Cases with an initial eGFR <30 mL/min. per 1.73 m2 excluded to minimise use of data from cases with advanced disease. It is recognised that this approach has the potential disadvantage of excluding cases with the most acute course.
- Cases with <6 months of follow-up were excluded to minimise unreliability in the estimation of the rate of renal function decline calculated over a short time, recognising this was likely to exclude the most acute and rapidly progressive cases.
- Those who cannot tolerate MM excluded.
- Those with proteinuria <0.5 g per 24 hrs. were excluded to ensure the inclusion of patients at risk of progression.
- Those with secondary causes of mesangial IgA deposits such as Henoch-Schönlein purpura or those with comorbid conditions such as diabetes mellitus were excluded.
- Those with crescentic glomerulonephritis in renal biopsy.

Pathology Definitions: By an iterative process, pathological lesions were defined, lesions with poor reproducibility among pathologists were excluded, and a simplified set of pathology variables was agreed that was suitable for further evaluation in IgAN.

Mesangial hypercellularity – in < or > 50% glomeruli	M0 or M1
Endocapillary hypercellularity – present/absent	E0 or E1
Segmental sclerosis/adhesions- present/absent	S0 or S1
Tubular atrophy/interstitial fibrosis – 0-25%, 26-50%, >50%	T0, T1 or T2.
Table 1	

Patients admitted during a time period from November 2009 to June 2010 with IgA Nephropathy are biopsied and scored according to Oxford MEST classification. Patients received MM with low-dose steroids (MM 20 mg/kg+ 10 mg prednisolone) for 6 months. Control arm received conventional therapy (Telmisartan 40 mg+ 5 mg Ramipril). After 6 months of therapy, patients are re-biopsied and graded according to MEST score. The treatment response is assessed.

Technical Data: Kidney biopsy and histopathology based on MEST scoring. Immunofluorescence studies for identifying immunoglobulin deposits were done. Periodic monitoring of drug related toxicities was done. Statistical analysis done using SPSS version 16. Independent sample T test, paired sample T test, one-way ANOVA and McNemar Chi-square tests were employed.

RESULTS: A prospective case controlled study for 8 months was conducted. In all, 48 patients were enrolled in the study, of which 2 were excluded during the course of the study. Of these 46, 32 of patients were given low-dose steroid + MM and 14 patients were given conventional treatment. Of the 46 subjects who were enrolled, 31 subjects were having M1 (<50% glomeruli) Mesangial hypercellularity while 15 subjects were having M0 (>50% glomeruli) Mesangial hypercellularity.

Endocapillary hypercellularity was present in 21 and absent in 25 subjects. Segmental sclerosis/adhesions were observed in 20 and absent in 26 subjects. (0-25%) Tubular atrophy/interstitial fibrosis was observed in 17 subjects, (26-50%). Tubular atrophy/interstitial fibrosis was observed in 20 subjects (> 50%). Tubular atrophy/interstitial fibrosis was observed in 9 subjects. Refer Table I for the mean proteinuria and mean eGFR.

Of the total enrolled 46 subjects, 32 were included in Group M (Low-dose steroid + MM treatment) and 14 were included in Group C (Conventional Treatment). The subjects in each group were assessed for Mesangial hypercellularity, Endocapillary hypercellularity, Segmental sclerosis/ adhesions and Tubular atrophy/ interstitial fibrosis.

Clinical Improvement after Treatment: In the subjects included in the Group M, it was observed that mean proteinuria decreased from 1650 mg to 900 mg, mean eGFR increased from 66 mL/min. to 72 mL/min. Microhaematuria decreased from 32 mg to 14 mg. Mean (Preproteinuria-postproteinuria) was 682.15 (p=.001). Mean (eGFR post-GFR pre) was 6.15 (p=.045). In the subjects included in the Group C, it was observed that mean proteinuria decreased from 1300 mg to 1050 mg (p=0.1), mean eGFR decreased from 72 mL/min. to 69 mL/min. (p=0.25). Microhaematuria decreased from 14 mg to 10 mg.

Side Effect Profile of MM: Gastrointestinal symptoms were observed in 15 (47%) patients while severe infections (> 1 hospital admissions) was observed in 1 (3%) patient.

There were neither severe gastrointestinal symptoms necessitating stoppage of drug nor was bone marrow suppression necessitating stoppage of drug.

DISCUSSION: IgA nephropathy is the most common glomerular disease worldwide. Although not described until 1968, this is the most common form of acute glomerulonephritis. As it represents a spectrum of severity it is possible that the mildest cases are not diagnosed. It is more common in people of European or Asian ancestry than those of African descent. It is about twice as common in males as in females. Primary IgAN is more frequent in males them in females.[1]

Primary IgAN presents with focal or diffuse mesangial hypercellularity and expansion of the extracellular matrix. Other glomerular lesions include focal on diffuse endocapillary proliferation, extracapillary proliferation, with crescent formation, glomerular hyalinosis, and segmental or global sclerosis. The hallmark of these forms of nephritis is IgA deposition together with high serum levels of IgA, mainly IgAl in polymeric form in more than 50% of patients. On the basis of these features, IgAN has been stratified in to five histologic classes (Haas Classification) in order of increasing severity of renal damage.[2]

The goal of this new system is to identify specific pathological features that more accurately predict risk of progression of renal disease in IgA nephropathy, thus enabling both clinicians and pathologists to improve individual patient prognostication. Renal biopsies from all patients were scored by pathologists blinded to the clinical data for pathological variables identified as reproducible by an iterative process. Four of these variables:

1. The mesangial hypercellularity score.
2. Segmental glomerulosclerosis.
3. Endocapillary hypercellularity and
4. Tubular atrophy/interstitial fibrosis were shown to have independent value in predicting renal outcome.[3]

Despite the ubiquity and progressive nature of the disease, no definite treatment is yet found to be curative in cases of progressive disease. Side effects of longterm corticosteroid use limit its use. However, no studies showing the histopathological resolution with this newer mode of therapy are available. The effectiveness of new drugs such as mycophenolate mofetil is still debated in adults; an RCT using this drug in children and young subjects is ongoing in the United States.[4]

CONCLUSION: The four variables of Oxford classification system for IgA Nephropathy detected on renal biopsy have been found to be independent prognostic factors for progression to renal disease. Mesangial hypercellularity and endocapillary hypercellularity have direct correlation with proteinuria. Segmental sclerosis, tubular atrophy and interstitial fibrosis are direct predictors of decrement in GFR.

Therapy with MMF and steroids is effective in retarding the proteinuria, microhaematuria and progression of the disease in IgAN. Therapy with MMF and steroids is effective in reversing the mesangial hypercellularity and endocapillary hypercellularity and preventing the progression of segmental sclerosis and tubular atrophy. Institution of immunosuppressive therapy in the early course of the disease is helpful in preventing the progression to chronicity.

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