EPIDEMIOLOGY AND CLINICAL OUTCOMES OF PATIENTS WITH IDIOPATHIC MEMBRANOUS GLOMERULONEPHRITIS AT GROOTE SCHUUR HOSPITAL OVER A TEN YEAR PERIOD

By

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AMHOLU001

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DECLARATION

I, Oluwatoyin Idaomeh Ameh, hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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FIGURES AND TABLES

Chapter 2

LIST OF ABBREVIATIONS

APOL1	Apolipoprotein-1
BSA	Body surface area
CNI	Calcineurin inhibitor
CR	Complete remission
DNH	Division of Nephrology and Hypertension
eGFR	Estimated glomerular filtration rate
EM	Electron microscopy
ESRD	End- stage renal disease
FSGS	Focal and segmental glomerulosclerosis
GN	Glomerulonephritis
GSH	Groote Schuur Hospital
HREC	Human research ethics committee
IF	Interstitial fibrosis
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IMGN	Idiopathic membranous glomerulonephritis
IQR	Interquartile range
ISP	Immunosuppressive
MDRD	Modification of Diet in Renal Disease
MGN	Membranous glomerulonephritis
mls/min/m^2	Mililitres per minute per metre squared
M-PLA2R1	M-type phospholipase A2 receptor 1
PR	Partial remission
SLE	Systemic lupus erythematosus
SSA	Sub- Sahara Africa
THSD7A	Thrombospondin type 1 domain-containing 7A

ABSTRACT

BACKGROUND

Glomerulonephritis is a common cause of end-stage renal disease (ESRD) in developing countries. Idiopathic membranous nephropathy (IMGN) is an identified cause of nephrotic syndrome in South Africa. Early attainment of complete remission (CR) or partial remission (PR) in patients with IMGN has been shown to slow progression to ESRD. There is a dearth of outcome studies in Africa on IMGN.

METHODS

This study was approved by the institution's Human Research Ethics Committee. It was a retrospective review of patients diagnosed (biopsy-proven) with IMGN at the Division of Nephrology and Hypertension, Groote Schuur Hospital, Cape Town, over a 10 year period. Secondary causes of MN were excluded in this study. Demographic, clinical, biochemical and histological records of such patients were retrieved for analysis. The trends in clinical and biochemical parameters over the course of follow-up from baseline were also determined. The primary outcome of interest was the attainment of a CR or PR at the last date of follow-up. Predictors of the composite of CR and PR at the last follow-up visit were assessed using univariate and multivariate Cox-Regression analysis. The trend in estimated glomerular filtration rate over the median duration of follow-up was evaluated as a secondary outcome.

RESULTS

There were 56 patients with histologic and clinical parameters compatible with the diagnosis of IMGN. There were 26/56 females (46.4%) with an overall mean age of 41.5±14.6 years. Forty-three (43) patients had subsequent follow-up care at our centre with a median duration of follow-up of 23.0 (13.0, 48.0) months. Sixteen patients (37.2%) were treated with immunosuppression (ISP) -combination of steroids and cyclophosphamide, and 81.4% received renin-angiotensin system (RAS) blockade. There were no statistically significant differences in demographic and clinical features of patients treated with or without ISP. Trends in level of proteinuria, estimated GFR and serum albumin concentrations were also not significantly different between the 2 groups. Eighteen patients (41.9%) reached CR or PR at the last visit. There were also no statistically significant

differences in demographic, clinical, histological, and biochemical characteristics of patients who had or had not achieved remission. The median time-to-remission of patients treated with or without ISP was similar - 48.6 and 48.7 months respectively (p=0.13) while the proportions of patients not reaching CR/PR at 1 year and 2 years were 94.6% and 80.8% respectively by Kaplan-Meier analysis. Gender, race and use of immunosuppression did not influence remission status (log rank p>0.05). On regression analysis, the predictors of CR/PR at last follow up visit were GFR [OR 1.01 (95%CI: 1.00 – 1.02); p=0.041] and systolic BP (OR 0.97 [95%CI: 0.95 – 0.99); p=0.036].

CONCLUSION

Remission outcomes with the current immunosuppressive treatment protocol for IMGN are delayed and poor. There is a need for its re-evaluation and also for longitudinal, multicenter studies to assess the best treatment approach (-es) to IMGN in South Africa.

CHAPTER 1: INTRODUCTION

1.1 CONTEXT

BACKGROUND

End stage renal disease continues to impose an increased burden on scarce health resources in sub-Sahara Africa (SSA) where there is a transition in epidemiology from the predominance of communicable diseases to the co-dominance of communicable and non-communicable diseases.[1,2] While diabetes mellitus is the leading cause of end-stage renal disease (ESRD) in industrialized societies, glomerulonephritis (GN) and systemic hypertension are the more prevalent causes of ESRD in SSA.[1]

GN may present clinically as a nephritic or a nephrotic syndrome. The spectrum of GN disorders associated with the nephrotic syndrome varies between children and adults with idiopathic membranous glomerulonephritis (IMGN) reported to be the commonest and second commonest cause of nephrotic syndrome in adults in Europe and the United States respectively.[3] Membranous GN has been reported to account for 11.6% of cases with nephrotic range proteinuria in South Africa.[4]

Membranous GN may occur as an idiopathic disease or may be secondary to the presence of other conditions such as infections, autoimmune diseases, malignancies and drugs.[5] The distinction between idiopathic and secondary MGN rests on the absence of an identifiable systemic cause after an exhaustive and systematic search. Systemic conditions associated with MGN include chronic viral infections such as Hepatitis B and C, systemic autoimmune disorders such as systemic lupus erythematosus (SLE), rheumatoid arthritis, IgG4-related systemic disease, syphilis, and malignancies such as non-Hodgkin lymphoma, lung, colon, and breast tumours.[5] Drugs such as gold, D-penicillamine, non-steroidal anti-inflammatory agents and mercury-containing compounds are also known secondary causes of MGN.[5]

Idiopathic membranous GN (IMGN) is second only to focal segmental glomerulosclerosis (FSGS) as a cause of primary nephrotic syndrome globally in all adults; it is however the commonest cause of primary nephrotic syndrome among Caucasian adults.[6,7] While the exact pathogenic mechanisms involved in idiopathic MGN are not completely defined, an autoimmune basis has been established with a number of target human glomerular antigens identified. These include neutral endopeptidase, M-type phospholipase A2 receptor 1(M-PLA2R1), and thrombospondin type I domain-containing 7A (THSD7A).[8,9] This glomerular disease is characterized by the presence of diffuse and global glomerular sub-epithelial deposits on microscopy- a rather unique characteristic which makes the diagnosis of MGN possible with only one glomerulus on microscopy.[6] Minimal to absent cellular proliferation and the predominance of IgG4 on immunofluorescence distinguish IMGN from secondary MGN.[6]

IMGN is the most common cause of nephrotic syndrome in all adults worldwide with a reported incidence rate of 1.2 /100,000/year.[10,11] Incidence rates have remained unchanged in almost half a decade.[11] IMGN is more common among males with a male to female distribution of 2:1.[12] It is a disease of adults with a peak incidence between the 3rd and 5th decades of life; IMGN rarely occurs in children.[5,13] It has no racial predilection with similar incidence rates among all racial groups. This is in contrast to what has been described in other primary glomerulonephritides such as primary/idiopathic focal segmental glomerulosclerosis (FSGS) in which there is a higher incidence among blacks, or IgA glomerulonephritis with a higher incidence among Asians.[14] However, variability in the regional incidence rates of IMGN has been noted and it is uncertain if this truly reflects regional disease distribution. Current regional differences in reported incidence rates are believed to reflect differences in access to diagnostic renal biopsy services with subsequent under-reporting of cases from disadvantaged regions.[11] IMGN can also occur in the renal allograft where it may occur either as a recurrent disease or a *de novo* disease.[6]

The natural history of IMGN has been classically described by the "rule of thirds" in which a third of patients enter into partial or complete remission, a third continue to have nephrotic-range proteinuria with a normal or impaired (but stable) renal function and a third progress to ESRD.[6] Young age, female gender, low-grade proteinuria, partial or complete remission, and Asian ancestry have been identified as favourable prognostic factors in IMGN.[15-17] The various management strategies for IMGN have thus been oriented towards maximizing the number of patients who go into some form of remission, and improving aspects of the natural history of the disease associated with poor patient outcome. These include retarding progression to ESRD and reducing the proportion of patients with continued proteinuria and its attendant complications.[18]

Reduction in proteinuria is known to retard the decline of renal function in non-diabetic proteinuric diseases.[19] Similarly, the occurrence of remission in IMGN patients is associated with improved renal survival.[20] These observations have thus placed premium on the value of remission of proteinuria as both a treatment target and an outcome measure in IMGN. While earlier studies of IMGN had demonstrated favourable renal and patient survival with the attainment of a complete remission of proteinuria, Troyanov et al have additionally demonstrated that attaining a partial remission of proteinuria in IMGN is associated with favourable long-term renal outcomes.[21] Partial remission is thus as compelling a management target as spontaneous remission in IMGN. Remission in IMGN may occur spontaneously or may be induced by the use of immunosuppressive therapy. It is known that spontaneous remissions occur the most in IMGN of all proteinuric glomerular disorders.[10] Spontaneous remissions are however less likely with increasing severity of proteinuria. Among a Spanish cohort of IMGN patients, the proportion of spontaneous remitters (complete or partial) declined from 37.1% to 21.5% as baseline proteinuria increased from a daily maximum of 8g/24hours to >12g/24hours.[22] The landmark immunosuppressive trial in IMGN patients by Ponticelli utilizing the alkylating agent Chlorambucil in combination with corticosteroids proved that remission rates can be increased to almost 90% among IMGN patients actively treated with immunosuppressive agents.[23]

The stabilization of renal function, and by extension the retardation of progression to ESRD, has been described as one of the ultimate goals of management in IMGN.[10] Renal survival during follow-up is hence a frequently observed outcome measure in studies among IMGN patients. Risk assessment and subsequent categorization into low, medium and high risk in IMGN is based on the likelihood of progression to ESRD.[15,24] Patients' risk of progression is determined by the composite of renal function and proteinuria at baseline. Beyond its use in grouping patients according to progression potential, risk categorization has also been used as a tool to guide the need for initiation of active (immunosuppressive) treatment in IMGN.[10] The role immunosuppressive therapy plays in stabilizing renal function decline and retardation of progression to ESRD has been variously established. ESRD-free survival rate was 92% after 10 years of follow-up among patients who had been actively treated with immunosuppression versus 60% who received only supportive care in the trial of alkylating agents in IMGN.[23] Similar trends in renal survival have also been shown when active treatment is targeted towards patients with an ab initio high risk of ESRD progression.[25]

The goals of treatment in IMGN include the preservation of renal function and prevention of the complications of the nephrotic syndrome.[18] Current guidelines recommend treatment for IMGN patients with nephrotic syndrome and any of urinary protein >4g/day, disabling or life-threatening symptoms of nephrotic syndrome or a rise in serum creatinine >30% over 6-12 months with an estimated glomerular filtration rate of ≥ 25-30mls/min/1.73m^2.[14] Available therapeutic agents include oral and intravenous corticosteroids, alkylating agents such as Cyclophosphamide and Chlorambucil, the calcineurin inhibitors (CNI) e.g. cyclosporine, tacrolimus, and biological agents such as Rituximab.

The various ISP agents available for the treatment of IMGN are combined into various regimens that are available for use in current clinical practice. While there are no head-to-head trials comparing the superiority or non-inferiority of the various regimens, a recent systematic review showed that the combination regimen of an alkylating agent with corticosteroid was significantly associated with

higher complete and partial remission rates, a reduction in all-cause mortality and ESRD. These benefits however come at the expense of an increased risk of therapy discontinuation and hospitalizations due to adverse events.[26]

Renal transplantation is a treatment option in iMGN patients who have progressed to ESRD. The disease may however emerge in the transplanted kidney either as a de novo disease (approximately 70% of cases) or as a recurrence of the primary glomerular disease.[6] Recurrence in the renal allograft may be as high as 42% and account for 12.5% of graft losses at 10 years.[27,28]

RATIONALE OF THE RESEARCH

If the tide of ESRD from GN is to be stemmed in Africa, it is imperative that clinical outcome data, in addition to epidemiologic data, be made available to influence appropriate health policy formulation and implementation. Some data is available in Africa describing the frequency of occurrence of IMGN as a cause of primary glomerulonephritis and nephrotic syndrome.[4,29] There is however a dearth of data in the literature describing the clinical characteristics and course of IMGN in South Africa, and indeed Africa as a whole. In addition, data is scarce on the outcomes of remission, renal survival, and patient survival in IMGN. The clinical outcomes of patients with secondary membranous GN from lupus nephritis from our centre has been previously described.[30]

We therefore sought to describe the clinical outcomes of IMGN among South African adults attending the Division of Nephrology and Hypertension of Groote Schuur Hospital over the 10-year period 1st January, 2003 to 31st December, 2013. Our specific objectives were:

1. To describe pattern of idiopathic membranous glomerulonephritis in our patient population of Africans,

2. To describe the clinical outcomes of patients with idiopathic membranous glomerulonephritis in our setting, and

3. To determine the association between baseline clinical characteristics and clinical outcomes in our cohort of idiopathic membranous glomerulonephritis patients.

RESEARCH SETTING

This study was carried out at the Division of Nephrology and Hypertension, Groote Schuur Hospital (GSH), Cape Town. GSH is one of two provincial government-funded, adult, academic tertiary health facilities that serve the central health district of the Cape Town Metro region.[31] The catchment population of the facility encompasses a diverse socioeconomic and cultural group. The study was a 10-year retrospective review of biopsy-proven IMGN in adults that had been diagnosed and managed within the Division of Nephrology and Hypertension at GSH. All adult IMGN patients from the period 1st January, 2003 to 31st December, 2013 were identified from the division's renal biopsy register.

1.2 ETHICAL CONSIDERATIONS

The ethical issues taken into consideration in this study relate to gaining access to protected patients' information contained within medical records, and the maintenance of confidentiality of such information obtained for the conduct of this study. Ethical approval was thus obtained from the Human Ethics Research Committee, University of Cape Town (HREC/REF: 046/2014).

1.3 AUTHOR GUIDELINES FOR THE *NEPHROLOGY DIALYSIS TRANSPLANTATION* JOURNAL

Author guidelines for article submission to the *Nephrology Dialysis Transplantation* Journal of the European Renal Association-European Dialysis and Transplantation Association [ERA-EDTA] (in their exact words) are attached in appendix 1.

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CHAPTER TWO: PUBLICATION-READY MANUSCRIPT

Out of Africa: Complete and Partial Remissions as a Combined Outcome in Patients with Idiopathic Membranous Glomerulonephritis in Cape Town

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Keywords: Membranous glomerulonephritis, immunosuppression, remission, South Africa

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ABSTRACT

Background: Idiopathic membranous glomerulonephritis (IMGN) is an identified cause of nephrotic syndrome in South African adults. Remission outcomes in affected patients remain unknown.

Methods: This was a retrospective review of patients with biopsy-proven IMGN over a 10 year period. Secondary causes of MN were excluded. Demographic, clinical, biochemical and histological records were retrieved for analysis. The trends in biochemical parameters from baseline were determined. The primary outcome was the attainment of a complete or partial remission (CR / PR) at the last follow-up.

Results: Fifty-six patients met the criteria for inclusion and 43 had subsequent follow-up care with a median duration of follow-up of 23.0 (13.0 - 48.0) months. Sixteen patients (37.2%) were treated with immunosuppression (corticosteroids and cyclophosphamide) and 81.4% received anti-proteinuric agents. There were no significant differences in demographic and clinical features of patients categorized by immunosuppression (ISP) use. Changes in level of proteinuria and estimated glomerular filtration rate (eGFR) were also not significantly different between the 2 groups. Eighteen patients (41.9%) reached CR or PR at the last visit. The median times-to-remission of patients according to ISP status were similar at 48.6 and 48.7 months respectively (p=0.104) while the proportions of patients not reaching CR/PR at 12 and 24 months were 94.6% and 80.8% respectively. Gender and race did not predict remission status (p>0.05). Predictors of CR/PR at last visit were eGFR [OR 1.01 (95%CI: 1.00 – 1.02); p=0.041], and systolic BP (OR 0.97 [95%CI: 0.95 – 0.99); p=0.036].

Conclusion: Remission outcomes in this African IMGN cohort are delayed and poor.

(248 words)

Keywords: Idiopathic Membranous glomerulonephritis, Remission, South Africa,

SHORT SUMMARY

Patient outcomes among Africans with idiopathic membranous glomerulonephritis is unknown. Remission outcomes in South Africans with the current immunosuppressive regimen is delayed and poor. There is the need to review the current treatment approaches to IMGN in Cape Town.

INTRODUCTION

Glomerulonephritis remains a prevalent cause of end-stage renal disease (ESRD) in Sub-Saharan Africa (SSA).[1] Idiopathic membranous glomerulonephritis (IMGN) is the commonest cause of primary nephrotic syndrome (NS) in adults and ranks as the third commonest cause of nephrotic range proteinuria in South African adult population.[2,3] It is considered to be a renal-limited autoimmune disorder in which autoantibodies are formed against one or more constituent podocyte autoantigens.[4] Two such autoantigens have been identified to date and include the phospholipase A_2 receptor and the thrombospondin type-1 domain containing 7A.[4,5] The specific pathogenetic mechanism that triggers autoantibody production remains unknown.

The natural history of outcomes in IMN has historically been described by the rule of thirds whereby a third of patients attain spontaneous remission, a third remain proteinuric, and a third progress inexorably to renal failure.[6] Clinical outcome studies have thus been oriented towards evaluating the modification of the natural history of IMGN with the use of immunosuppressive (ISP) medications, and also determining the best ISP regimen to achieve this. Study findings have not been consistent in supporting an obligatory role for ISP treatment. It has been demonstrated that approximately 50% of untreated patients will develop spontaneous or partial remission of proteinuria - a phenomenon that has also been demonstrated among untreated IMGN patients with renal impairment at diagnosis.[7,8]

The debate on the need for immunosuppressive treatment in IMGN has centered on the role such treatment plays in altering patient outcomes and determining the appropriate candidate in whom remission would otherwise not be achieved without the use of immunosuppression.[9,10] Remission attainment and renal survival are the best and accepted outcome measures in IMGN.[2] Outcome studies in the era of immunosuppression addressing these endpoints have shown benefit in nephrotic IMGN patients with and without renal

impairment at the initiation of therapy.[11,12] There is a paucity of outcome data in adults with IMGN in SSA and we therefore sought to describe the clinical characteristics and remission outcomes in patients with biopsy-proven IMGN at our centre. The primary outcome of interest was the composite of complete and partial remission with respect to immunosuppression use. The change in estimated glomerular filtration (eGFR) rate over time in relation to remission status was evaluated as a secondary outcome.

SUBJECTS AND METHODS

The study was approved by the Human Research Ethics Committee of the University of Cape Town (HREC/REF: 046/2014).

Patients

Patients with IMGN were identified from the renal biopsy registry of the Division of Nephrology and Hypertension (DNH), Groote Schuur Hospital (GSH), University of Cape Town. The case records of all biopsy-proven IMGN patients who were treated and followed up between 1st January, 2003 and 31st December, 2013 at the DNH were subsequently retrospectively assessed. Probable secondary causes of Membranous GN were thoroughly sought from serologic work-up for systemic lupus erythematosus, testing for chronic infections such as chronic hepatitis B infection, syphilis, and a work-up for malignancy. Individuals with documented positive tests were excluded.

Data collection

Demographic, biochemical and clinical data were collected at the time of the diagnostic renal biopsy and at subsequent visits until the last visit within the study duration, or occurrence of death. Demographic data collected include age, gender and race while clinical and biochemical data collected at each of these time points include systolic blood pressure (SBP), diastolic blood pressure (DBP), serum creatinine, eGFR using the MDRD 4-variable equation, and 24-hour urinary protein excretion by a spot urine protein-creatinine ratio determination. Anti-phospholipase A2 receptor 1 (PLA2R1) antibodies assessment was not done due to unavailability of stored sera.

All immunosuppressive therapies administered were documented. All patients who received immunosuppression got initial therapy according to the unit protocol [1g Methylprednisone

followed by Prednisone 40mg daily for one month alternating with monthly intravenous (IV) cyclophosphamide 750mg/m^2 body surface area (BSA) for 6 months with steroid taper to 10mg at 6 months]. Probable complications from all medications given and known complications of IMGN, other than renal insufficiency, were also reviewed.

Definitions

- Glomerular filtration rate was estimated using the 4-variable modification of diet in renal disease (MDRD) equation.[13]
- A complete remission was defined as proteinuria ≤ 300mg/day and a partial remission defined as proteinuria <3.5g/day with a reduction from its peak value by 50%.[14] Remission status was allocated if either partial or complete remission criteria were met and if eGFR was > 15mls/min.[14]
- Nephrotic syndrome at presentation was defined as proteinuria ≥ 3.5g/day with serum albumin < 30g/L.
- Time to remission was determined from the time of the diagnostic kidney biopsy.

Use of immunosuppressive agents was reported as intent-to-treat irrespective of duration of therapy.[14] Patients were categorized into two groups based on treatment with immunosuppression. Actual immunosuppressive therapy received consisted of at least 30mg of prednisone with or without Methylprednisone monthly alternating with 750mg/m^2 BSA of IV cyclophosphamide; no patient had monotherapy. The use of warfarin, RAAS blockade and antihypertensives was categorized by exposure status.

Histology

The diagnosis of IMGN was made based on typical light microscopy findings of spikes on silver-methenamine stain, immunocytochemistry findings of IgG and C3 in the peripheral capillary loops, and electron microscopy (EM) findings of sub-epithelial deposits. Histologic

staging of glomerular basement membrane thickening into stages I-IV was done according to the criteria by Ehrenreich et al, while interstitial fibrosis (IF) was graded as absent, mild, moderate or severe.[15]

Statistical analysis

Data analysis was performed using Stata® 13 software (Stata Corp, Texas). Continuous variables were expressed as mean ± standard deviation for normally distributed variables and median (interquartile range [IQR]) for non-parametric continuous variables; comparisons were made using an independent sample student's t-test or a Wilcoxon rank-sum test where appropriate. Categorical variables were presented as frequencies and percentages with comparisons made using a Chi-square test or Fisher's exact test where appropriate. Analyses of response profiles were utilized to assess the trend of proteinuria and eGFR over time and the predictors of observed trends.

Time-to-remission analysis was done using Kaplan-Meier survival analysis. Time-to-remission estimates were compared between groups by log-rank test after censoring for loss-to-follow up. Multivariate Cox proportional hazards regression analysis (utilizing selected covariates from univariate analysis) was used to determine possible predictors of remission. A p-value of <0.05 was considered statistically significant.

RESULTS

Demographic, clinical and biochemical features at baseline

Ninety-two patients had a histologic diagnosis of membranous glomerulonephritis. Thirty-six patients with identified secondary causes of membranous GN were excluded (Figure 1). As shown in Table 1 among the 56 patients identified as IMGN at biopsy, 43 (77.0%) had nephrotic syndrome at presentation. Mean age at presentation was 41.5 ±14.6 years, 46.4% were females and 37.5% were blacks. Median serum creatinine at presentation **was** 79.5 (IQR 61.5, 118.0) μmol/L, with a median eGFR of 88.4 (IQR 60.0-134.8) mls/min/1.73m^2. Median UPCR was 0.98 (IQR 0.66, 1.37) g/mmol with a mean serum albumin of 19.1 ±7.0 g/L for the entire group. The average number of glomeruli obtained at biopsy was 12.7 ± 7.8 with the most frequently occurring EM stage of IMGN being stage 2 (34.9%) The highest number of sclerosed glomeruli in a single biopsy was 8 (min, max 0, 8) and IF was demonstrable in 43.1% of biopsies (Table 2).

Baseline characteristics of patients followed up at the DNH-GSH

Thirteen (13) patients who were followed up at other health facilities were excluded from further analysis. Forty-three (43) patients were followed up at DNH-GSH with a median follow-up of 23.0 (13.0 - 48.0) months. The patients were stratified according to treatment with baseline characteristics shown in Table 3.

There was an equal distribution of black African patients between groups of patients treated and those not treated with ISP. Patients treated with ISP were older (46.3 ± 15.7 years vs 40.2 ± 15.7; p=0.20), had higher SBP (133.2 ± 3.9 mmHg vs 128.8 ± 3.6 mmHg; p=0.43) and had a higher proportion of prevalent hypertensives (43.8% vs 25.0%; p=0.19). Baseline eGFR was lower among the ISP-treated patients (89.3 ± 10.8 mls/min/1.73m^2 vs. 113.0 ± 11.5 mls/min/1.73m^2, p=0.17); urinary protein excretion was higher in the ISP-treated group (1.12

± 0.11g/mmol). ISP-treated patients were more likely to present with nephrotic syndrome (93.8% vs 63.0%, p= 0.025) as they were also to present with a complication of nephrotic syndrome - mainly thromboembolic phenomena and infection. Angiotensin converting enzyme inhibitor (ACEi) therapy was instituted in at least 80% of patients in either treatment group (Table 3).

Immunosuppressive therapy and outcomes

All patients who received ISP received corticosteroids and cyclophosphamide. They were initiated on ISP after a period of conservative therapy with a median time to ISP initiation of 6.0 (IQR 1.8-9.8) months. The mean cumulative dose of cyclophosphamide given was 5.5 ± 2.9g. No patient got corticosteroid alone as initial therapy however 6 (14.0%) patients remained on low-dose oral corticosteroid at the last follow-up visit. Fifty percent (50.0%) of patients who received ISP therapy attained a partial or complete remission while 37.0% of patients who were conservatively managed attained either a partial or complete of remission, p=0.62 (Table 4).

Trend of Proteinuria Response

Figure 2 shows the proteinuria trend according to treatment category. Within ISP-treated patients there was a persistent decline in proteinuria at 12 months [-0.49 (CI -0.90 to -0.08) g/mmol, p=0.020) and 24 months (-0.62 (CI -1.10 to -0.13) g/mmol, p=0.013) from baseline. Similar significant trends were observed in the non-ISP group; there was therefore no significant between-groups difference in proteinuria decline over the duration of follow-up (p=0.97).

Time-to-Combined Remission Analysis

The combined end-point of complete and partial remissions was analysed in the time-to-remission analysis. The cumulative composite remission curve for the entire group is presented in Figure 3a. At 12- and 24-months respectively, 94.6% and 80.8% of all IMGN patients had not attained the combined end-point. Figure 3b shows the survival curves according to ISP status. ISP-treated patients had earlier remission rates, 13.3% in the first 12 months in comparison to 0% remission events in the same period among the non-ISP treated group. At 24 months, 31.7% (CI: 12.9%-65.2%) of patients in the ISP group and 10.4% (CI: 2.8%-37.3%) in the non-ISP group had attained the combined end-point. The median times-to-remission of the groups were however similar at 48.6 (IQR 21.8-71.2) months and 48.7 (IQR 33.3- 88.1) months, p=0.104 respectively (Figure 3b).

Univariate Cox regression analysis showed that individuals in the ISP group were twice as likely to attain the composite end-point (HR 2.22, 95% CI =0.8 - 6.0, p=0.11). SBP was a predictor of composite remission at last visit (HR 0.97 [95% CI 0.95-0.99], p=0.039) and for every 10mmHg increase in SBP at last follow-up there was an associated 25% reduction in the hazard of the composite endpoint (HR 0.75 [95% CI 0.58-0.98]). Likewise eGFR at last visit was significantly associated with outcome (HR 1.01 [95% CI 1.001-1.023], p=0.041) with every 10mls/min increase in eGFR at last follow up increasing the hazard of the endpoint by 12% (HR 1.12 [95% CI 1.005-1.254]). Neither eGFR at the time of biopsy (HR 1.00 [95%CI 0.99-1.01], p=0.73) nor systolic blood pressure at biopsy (HR 0.99 [95%CI 0.96-1.02], p=0.73) was predictive of remission at last visit. Race, gender, IF at biopsy, EM-grade of IMGN and prevalent hypertension at biopsy were not significantly predictive of the hazards of combined remission at last follow up (Table 5). No multivariate Cox model significantly predicted combined remission.

Change in estimated glomerular filtration rate according to remission status

The eGFR trend of subjects according to remission category at last follow-up visit is depicted in figure 3. There was a trend towards a significant difference in the eGFR profile over time between subjects with the composite outcome of complete and partial remission, and those who had not attained remission (p=0.06). In assessing eGFR trends within each group, there was no statistically significant decline in renal function relative to baseline eGFR at 6, 12 and 24 months among those who achieved the composite outcome. In those who had not achieved any form of remission at the last follow up, eGFR decline relative to baseline was the most significant at 12 months (-18.4mls/min [95% CI: -33.0mls/min to -3.7mls/min], p=0.014).

DISCUSSION

The overarching aim in the management of persistent proteinuric disorders is the prevention of renal function deterioration and progression to ESRD.[16,17] Declining proteinuria in IMGN with the subsequent attainment of a complete or partial remission is known to correlate with better renal survival.[14,18] The use of remission categories as endpoints in observational and experimental studies of IMGN is therefore commonly observed. In our retrospective review of the combined remission outcomes of either a complete or partial remission among patients managed with IMGN at GSH in Cape Town, we found poor remission rates at last follow-up visit of 41.9% among all patients, and 43.8% among patients with the nephrotic syndrome. Median time-to-remission was similar among actively and conservatively treated patients. Race, gender, and presence of IF at biopsy did not significantly influence time-to-remission. Both SBP and eGFR at last visit were predictive of remission. An evaluation of renal function over the duration of follow-up utilizing eGFR trends demonstrated a propensity towards stabilization of renal function among patients who attained any form of remission. Conversely, the most significant mean decline in eGFR of -18mls/min was observed at 12 months of follow-up among subjects who had not attained any form of remission. To the best of our knowledge, this is the first remission outcome study of IMGN-only patients in Africa.

In a 10-year follow-up review of patients who had been randomized to immunosuppressive treatment with steroids and an alkylating agent, Ponticelli and colleagues reported a combined remission rate of 48.1% rate which compares to the rate in our study.[19] Troyanov et al in a Canadian cohort had achieved a 68% combined remission rate among IMGN patients with the nephrotic syndrome and in comparison, our remission rate of 43.8% is less favourable.[14] Patients in both cohorts (Troyanov and ours) had mean ages within the 4th decade of life however 61% of their patients had been treated actively with at least one form of immunosuppression while only 46.9% had received active treatment in the Cape Town

group. The lower proportion of patients actively treated in our group may thus have accounted for this discrepancy. African ancestry has been established to be associated with a higher risk for kidney disease.[20] Recently as well, APOL1 genetic susceptibilities have been shown to be associated with worse pathologic patterns in PLA2R1-associated IMGN in patients of African ancestry, and possibly play a role in clinical response.[21] We propose that racial differences may thus be an additional and plausible reason for the differences we observe between this African cohort and other Caucasian cohorts. Indeed, it is known that Japanese patients with IMGN fare much better than their Caucasian counterparts.[22] The added role of epigenetics in this variability needs further evaluation.

Median time-to-composite remission in our study was prolonged at 48.6 months. Shorter times have been reported. In a 12-year review by McQuarrie et al, times to PR and CR were 16.8 and 42.0 months respectively irrespective of treatment approach.[23] Similarly, in Canada, times to PR and CR were 23 and 30 months respectively. These studies however consisted solely of patients with nephrotic syndrome. In contrast, 74.0% of our patients were nephrotic. Notably, our patients at baseline had a higher degree of proteinuria than any of the Western groups. This, in addition to our definition of partial remission, which requires an additional 50% decline in the peak urinary protein value, would translate to longer transition times to remission. The clinical utility of proteinuria as an indicator of remission has been challenged by recent observations in anti-PLA2R antibodies-positive patients in whom remission of proteinuria lags behind the remission of anti-PLA2R antibodies by as much as 15 months.[24] We could not assess this phenomenon in our patients as the discovery of this antibody is a relatively recent discovery and there were no stored sera available for testing in our cohort.

The use of immunosuppression did not significantly reduce the median time-to-remission which was 48.6 months among those immunosuppressed and 48.7 months in those conservatively managed in our study. This is similar to what has been described among larger

samples of Caucasian patients whereby ISP treatment did not significantly predict remission outcomes.[14,23] In the setting of randomized clinical trials evaluating the role of ISP in inducing remission, highly significant differences have been shown based on treatment assignment. In the trial of Chlorambucil and Prednisone for IMGN, median time-to-remission was as short as 12 months in the actively treated arm with 5-year Kaplan-Meier remission estimates of 80%. Such highly statistically significant remission estimates have however not been consistently demonstrated in observational studies, our study inclusive. The highly restrictive patient selection criteria into these RCTs (which do not usually typify patient populations in clinics) may also explain these discrepancies. Our observation of non-significant differences according to treatment status should also be regarded in the context of similar degrees of proteinuria at baseline between the ISP and non-ISP treated. The ISP regimen used in our patient cohort could also account for the lack of demonstrable treatment effect. Our cyclophosphamide-based protocol substitutes oral cyclophosphamide with IV cyclophosphamide in order to reduce the cumulative dose of administered drug. This substitution has been occasioned by the increased risk of infectious complications with cyclophosphamide in our setting. Among lupus-nephritis patients induced with oral cyclophosphamide at our centre, 37.5% of deaths were sepsis-related.[25]

Protagonists for the use of ISP argue that beyond remission induction and renal function preservation, ISP use hastens the decline in proteinuria thus protecting IMGN patients from complications of the disease such as thromboembolic phenomena.[26] Indeed in the course of follow-up 31.3% of IS-treated patients in our study developed a complication of nephrotic syndrome (Table 3).

ESRD is a known consequence of IMGN and preventing its occurrence has been a major compelling indication for ISP treatment in IMGN. Although our study had a short follow-up time (relative to the natural history of IMGN) within which to evaluate renal survival with

certainty, we demonstrated a trend in renal function stabilization among patients who attained any form of remission irrespective of treatment category. This trend is in agreement with the known relationship between remission status and renal prognosis.[27] Troyanov and colleagues reported a 100%, 90%, and 45% 10-year renal survival respectively among patients who had attained complete, partial and no remission.[14] In determining the factor(s) predictive of our demonstrated trend, eGFR at baseline was predictive in univariate analysis; baseline eGFR remained an independent predictor on multivariate analysis that had assessed additional predictors (supplementary Table 1). The short median duration of follow up could have accounted for the demonstrated lack of association between renal function and other known predictors (supplementary Table 1). Renal function at baseline is a well-recognized predictor of renal outcome in IMGN so much so, it is one of the variables in the validated predictive risk scores of IMGN outcome. [28-30]

The retrospective design of the study and small sample size constrained this study's power to influence change in current practice. It however generates a number of hypotheses which can be tested prospectively. These include the optimal ISP regimen for IMGN among African patients in relation to short term outcomes such as remission induction and the long term outcome of renal survival. The relatively short duration of follow-up was also a limitation in assessing relapse among those who had attained remission, and also in describing ESRD outcomes.

Remission outcomes with the current ISP treatment protocol for IMGN are delayed and poor. There is a need for its re-evaluation to assess the best treatment approach (-es) to IMGN in South Africa.

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- Prof Pierre Ronco, Department of Nephrology and Dialysis, Hôpital Tenon, Paris, France, for his insightful review of this manuscript.

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TRANSPARENCY DECLARATIONS

None to declare.

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TABLES

Table 1. Baseline demographic, clinical and biochemical features of all idiopathic membranous glomerulonephritis patients

Baseline Characteristic	Patients, N=56
Age (years)	41.5 ± 14.6
Female n (*%)*	26 (46.4%)
Black n (*%)*	21 (37.5%)
SBP (*mmHg)*	130.1 ± 18.2
DBP (*mmHg)*	79.7 ± 11.5
Creatinine at diagnosis (*µmol/L)*	79.5 (IQR: 61.6 - 118.0)
eGFR *(mls/min)*	88.6 (IQR: 60.0 - 134.8)
Median uPCR *(g/mmol)*	9.8 (6.6-13.7)
Mean Albumin (g/L)	19.1 ± 7.0
Mean Cholesterol (*mmols/L)*	10.0 (7.3, 12.4)
Nephrotic syndrome n (%)	43 (76.7)

SBP- systolic blood pressure, DBP- diastolic blood pressure, eGFR-estimated glomerular filtration rate, IQR- interquartile range, uPCR-spot urine-to-creatinine ratio.

Table 2. Histologic findings of all patients at the time of biopsy

CHARACTERISTICS	VALUE
Number of glomeruli *mean, SD*	12.7 ± 7.8
Sclerosed glomeruli *median (min, max)*	0 (0,3)
EM grading *n/N (%)*	
Grade 1	6/47 (12.8)
Grade 2	16/47 (34.0)
Grade 3	10/47 (21.3)
Grade 4	15/47 (31.9)
Interstitial fibrosis *n/N (%)*	
Normal	29/51 (56.9)
Mild	18/51 (35.3)
Moderate	2/51 (3.9)
Severe	2/51 (3.9)

SD-standard deviation, min-minimum, max-maximum, EM – Electron microscopy

Table 3. Baseline characteristics of patients followed up

	Immunosuppression	**No immunosuppression**	**p-Value**
	N=16	**N=27**	
Age (years)	46.3 ± 13.7	40.2 ± 15.7	0.20
Female *n (%)*	7 (43.8%)	13 (48.2%)	0.52
Black *n (%)*	5 (31.3%)	9 (33.3%)	0.88
SBP (*mmHg*)	133.2 ± 3.9	128.8 ± 3.6	0.43
DBP (*mmHg*)	77.7 ± 3.0	81.0 ± 2.1	0.37
Hypertension *n (%)*	7 (43.8%)	6 (25.0%)	0.19
sCreatinine (*µmol/L)*	123.4 ± 35.7	83.5 ± 7.6	0.23
eGFR *(mls/min)*	89.3 ± 10.8	113.0 ± 11.5	0.17
sAlbumin (g/L)	20.1 ± 1.1	19.8 ± 1.7	0.89
UPCR *(g/mmol)*	1.12 ± 0.11	1.06 ± 0.16	0.75
ACEi *n (%)*	13 (81.3%)	22 (95.7%)	0.15
Statins *n (%)*	14 (87.5%)	18 (66.7%)	0.64
Nephrotic syndrome *n (%)*	15 (93.8)	17 (63.0)	0.025*
Complications of nephrotic syndrome *n (%)*	5 (31.3%)	2 (7.4%)	0.021*[#]

* P< 0.05, SBP- systolic blood pressure DBP- diastolic blood pressure, eGFR-estimated glomerular filtration rate, uPCR-spot urine-to-creatinine ratio, ACEi- angiotensin converting enzyme inhibitor; [#]Fisher's exact test

Table 4. Remission outcomes according to therapy

	Immunosuppression	**No immunosuppression**	**p-Value**
	N=16	**N=27**	
Remission status *n (%)*			
Complete	2 (12.5%)	4 (14.8%)	P= 0.62
Partial	6 (37.5%)	6 (22.2%)	
None	8 (50.0%)	17 (63.0%)	

Table 5. Univariate Cox regression analysis for selected predictors of the endpoint of any remission

Variable	HR	95% CI	P Value
Age	1.01	0.97- 1.04	0.61
Race (Black)	1.04	0.38 – 2.84	0.93
Gender (Male)	1.46	0.54 – 3.96	0.45
Interstitial fibrosis (Present)	1.59	0.50 – 4.48	0.38
eGFR at biopsy	1.00	0.99 - 1.01	0.73
SBP at biopsy	0.99	0.96 - 1.02	0.59
DBP at biopsy	0.99	0.94 - 1.05	0.74
eGFR last follow-up	1.01	1.001 - 1.02	0.041
SBP at last follow-up	0.97	0.94 - 0.99	0.036
DBP at last follow-up	0.98	0.95 - 1.01	0.24

eGFR - estimated glomerular filtration rate; SBP-systolic blood pressure; DBP-diastolic blood pressure

Supplementary Table 1. Multivariate model of trend in estimated glomerular filtration

	Coefficient	95% CI	p Value
eGFR at biopsy	0.89	0.77-1.007	0.001
Race (black)	4.54	-7.11 – 16.19	0.45
Gender (Female)	10.07	-0.63 -20.76	0.07
Interstitial fibrosis	1.19	-11.03-3.41	0.85

*eGFR- estimated glomerular filtration rate

LEGENDS TO FIGURES

Figure 1. Patient selection flow-chart

Figure 2. Proteinuria response profile according to immunosuppression status

Figure 3. Kaplan-Meier curves for time to any remission

(a) Entire group

(b) By immunosuppression use

Figure 4. Estimated glomerular filtration rate profile by remission status

Figure 1. Patient selection flow-chart

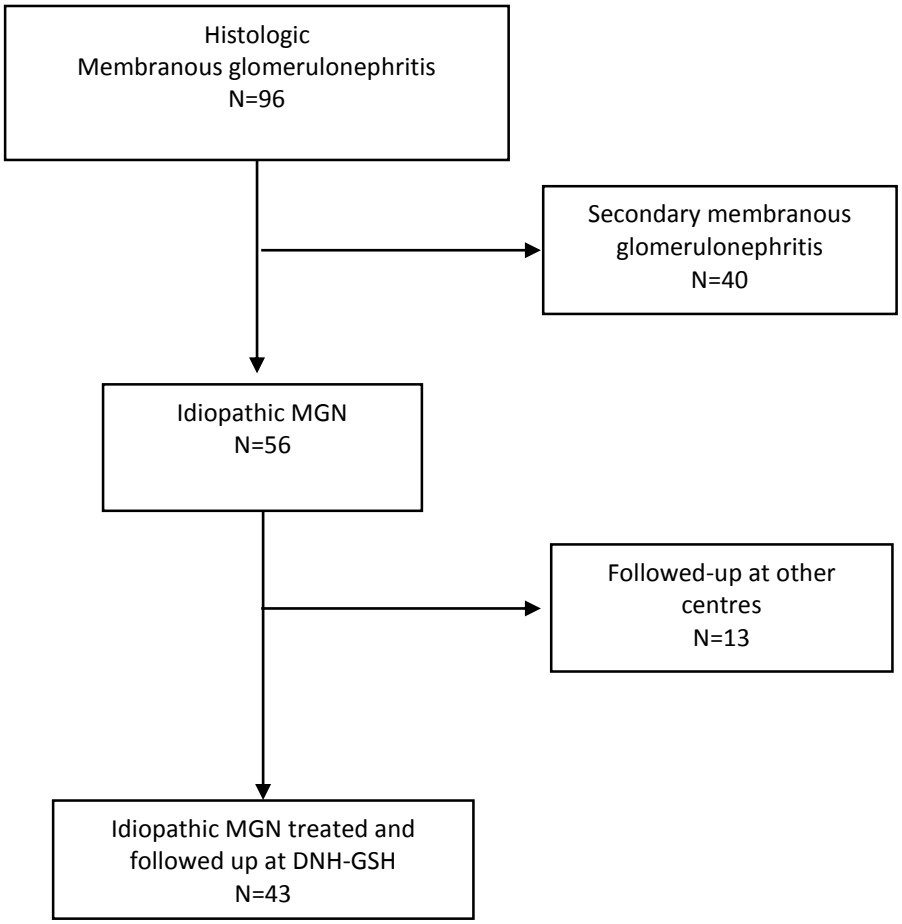


Figure 2. Proteinuria response profile according to immunosuppression status

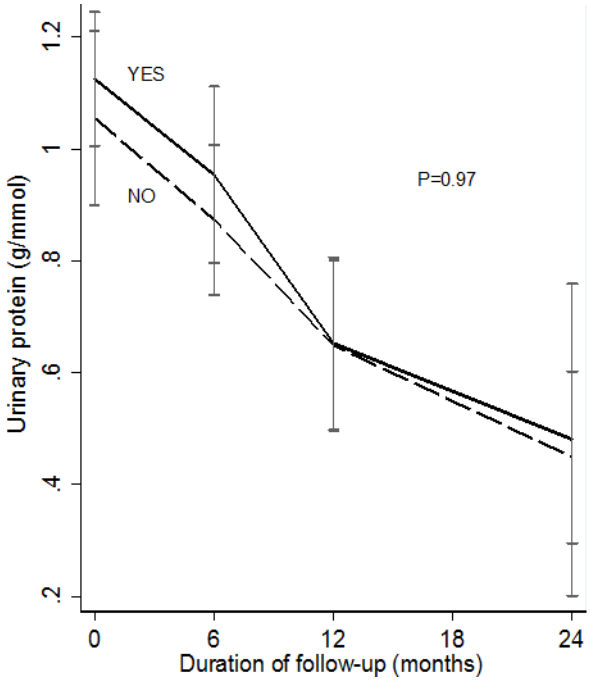


Figure 3. Kaplan-Meier curves for time to any remission

(a) entire group (b) by immunosuppression use

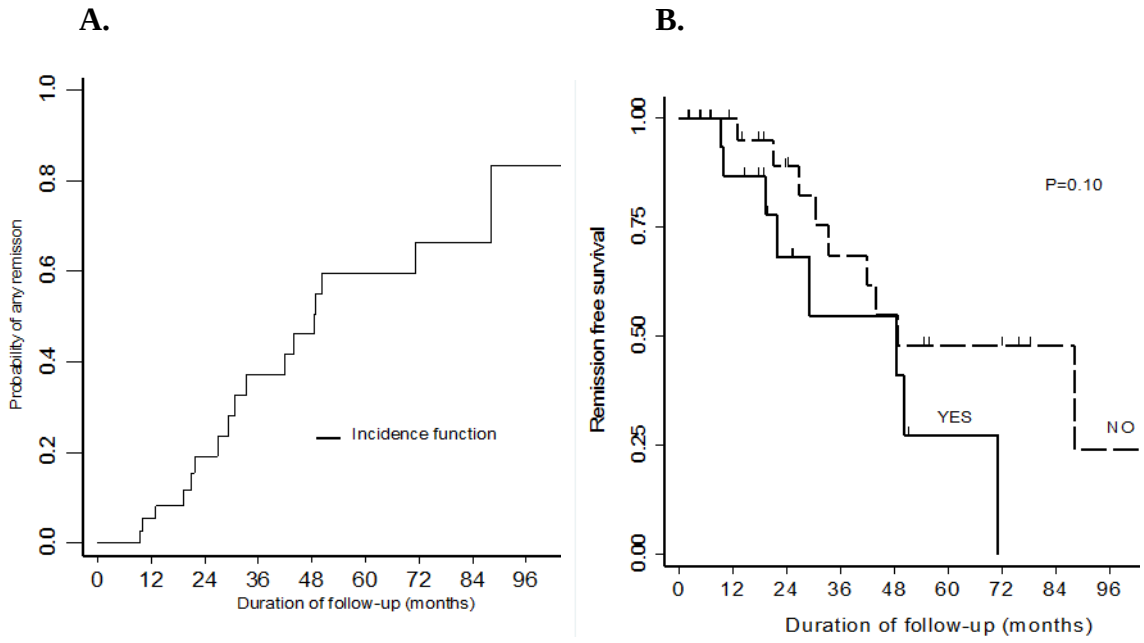
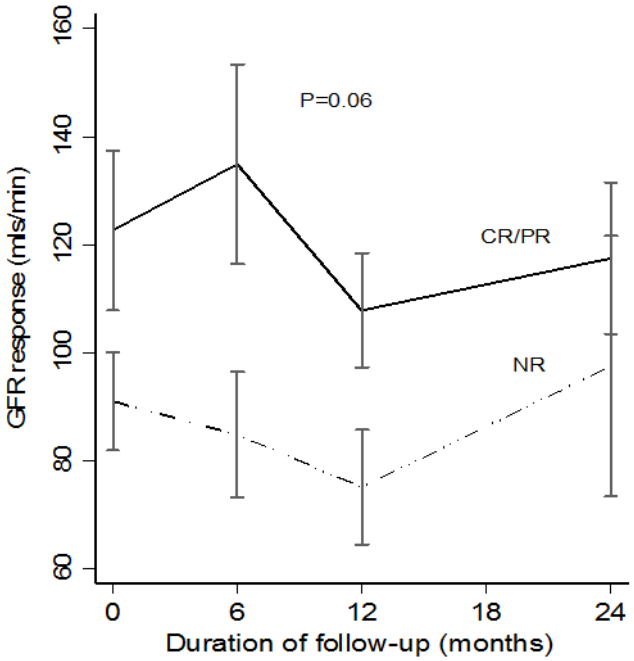


Figure 4. Estimated glomerular filtration rate profile by remission status



CR-complete remission; PR; Partial remission

APPENDICES

Appendix 1: *Nephrology Dialysis Transplantation (NDT)*-Basic and Clinical Sciences Journal Instruction to Authors of Original Articles

Aims and Scope of the Journal

NDT – Basic and Clinical Science is an official publication of the European Renal Association-European Dialysis and Transplant Association. *NDT* publishes Editorials, Reviews and original research. The journal covers the whole territory of nephrology research including experimental work in animal models and molecular biology studies. In the Clinical Science section we consider clinical trials (RCT have a priority in our journal), observational studies at large and original works on health economy as applied to nephrology. We aim to cover the whole spectrum of kidney disease research, from clinical nephrology to haemodialysis and peritoneal dialysis as well as renal transplantation.

Authors' role and responsibility

Each author should have participated sufficiently in the work to take public responsibility for the content.

Manuscripts should bear the full name and address, with telephone, fax, and email of the author to whom the proofs and correspondence should be sent (corresponding author). For all authors, first name and surname should be written in full.

In a covering letter, the individual contribution of each co-author must be detailed. This letter must contain the statement: 'the results presented in this paper have not been published previously in whole or part, except in abstract form'. Should your manuscript be accepted for publication, you will be required to give signed consent for publication

Preparation of the Manuscript to be submitted in NDT

Word count: maximum 3500 words, including abstract but excluding references, tables and figures.
Keywords: maximum 6
References: maximum 60

The order of original articles should be as follows:

1. Title page including the title (please bear in mind that we prefer a title to be concise yet eye-catching) and details of all authors, including first or given name, and affiliation;

2. On a separate page an abstract of ~250 words. It should consist of four paragraphs labelled `Background', `Methods', `Results' and `Conclusions'. They should briefly describe, respectively, the problems being addressed in this study, how the study was performed, the salient results and what the authors conclude from the results.

3. Keywords: no more than 6, in alphabetical order, characterizing the scope of the paper, the principal materials, and main subject of work.

4. Provide a short summary of max 3-4 sentences pointing out the main message of the paper.

5. On a new page: Introduction, Subjects and Methods, Results, Discussion, Acknowledgements, References, Tables, Legends to figures and Figures. All pages should be numbered consecutively

commencing with the title page. Headings (Introduction; Subjects and Methods, etc) should be placed on separate lines. It is important that authors number their pages prior to submission as reviewers will refer to particular pages when providing their comments on the manuscript.

Any statistical method must be detailed in the Subjects and Methods section, and any not in common use should be described fully or supported by references.

Abbreviations

Authors should not use abbreviations in headings and figure legends should be comprehensive without extensive repetition of the Subjects and Methods section. Authors are advised to refrain from excessive use of uncommon abbreviations, particularly to describe groups of patients or experimental animals.

References

The references should be numbered in the order in which they appear in the text. References to published abstracts should be mentioned in the text but not in the reference list.

At the end of the article the full list of references should give the name and initials of all authors unless there are more than six, when only the first three should be given followed by et al. The authors' names should be followed by the title of the article, the title of the Journal abbreviated according to the style of Index Medicus, the year of publication, the volume number and the first and last page numbers. References to books should give the title of the book, which should be followed by the place of publication, the publisher, the year and the relevant pages.

EXAMPLES
1. Madaio MP. Renal biopsy. Kidney Int 1990; 38: 529-543

Books:
2. Roberts NK. The cardiac conducting system and the His bundle electrogram. Appleton-Century-Crofts, New York, NY: 1981; 49-56

Chapters:
3. Rycroft RJG, Calnan CD. Facial rashes among visual display unit (VDU) operators. In: Pearce BG, ed. Health hazards of VDUs. Wiley, London, UK: 1984; 13-15

Note: In the online version of NDT, there are automatic links from the reference section of each article to Medline. This is a useful feature for readers, but is only possible if the references are accurate. It is the responsibility of the author to ensure the accuracy of the references in the submitted article. Downloading references direct from Medline is highly recommended.

Tables and Figures Preparation

All tables must be numbered consecutively and each must have a brief heading describing its contents. Any footnotes to tables should be indicated by superscript characters. Tables must be referred to in the main text in running order. All tables must be simple and not duplicate information given in the text.

Please be aware that the requirements for online submission and peer review, please upload your figures either embedded in the word processing file or separately as low-resolution images (.jpg, .tif, .gif or. eps).

Supplementary Material

Supporting material that is not essential for inclusion in the full text of the manuscript, but would nevertheless benefit the reader, can be made available by the publisher as online-only content, linked to the online manuscript. Such material should not be essential to understanding the conclusions of the paper, but should contain data that is additional or complementary and directly relevant to the article content. Such information might include more detailed methods, extended data sets/data analysis, or additional figures (including colour).

All material to be considered as Supplementary material must be submitted at the same time as the main manuscript for peer review. It cannot be altered or replaced after the paper has been accepted for publication. Please indicate clearly the material intended as Supplementary material upon submission. Also ensure that the Supplementary material is referred to in the main manuscript where necessary.

Transparency Declaration and Ethics

All authors must make a formal declaration at the time of submission indicating any potential conflict of interest. This is a condition of publication and failure to do so will delay the review process. Such declarations might include, but are not limited to, shareholding in or receipt of a grant, travel award or consultancy fee from a company whose product features in the submitted manuscript or a company that manufactures a competing product.

In addition, in the interests of openness, ALL papers submitted to NDT MUST include a 'Transparency declarations' section (which should appear at the end of the paper, before the 'References' section) within the article. We suggest authors concentrate on transparency declarations (i.e. conflicts of interest) of a financial nature, although relevant non-financial disclosures can also be made.

Appendix 2: Ethics Approval Letter

UNIVERSITY OF CAPE TOWN

Department of Medicine

Division of Nephrology and Hypertension

Dr. Ikechi G. Okpechi

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13th February 2014

Prof. Marc Blockman,
Chair - Human Research Ethics Committee
University of Cape Town

HREC/REF: 046/2014

PROTOCOL TITLE: ***"Epidemiology and clinical outcomes of patients identified with idiopathic membranous glomerulonephritis (MGN) at Groote Schuur Hospital over a 10 year period"***

Dear Prof Blockman,

We have recently received approval for the above study. However, after careful evaluation, we have decided to use this study for a degree purpose **(MPhil in Nephrology)** for one of the senior registrar (**Dr. Oluwatoyin Ameh**) in our division.

She was originally listed as a collaborator in this study. Study related activity will commence on approval of this change.

Many thanks for your assistance.

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

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Observatory 7925
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Website: www.health.uct.ac.za/research/humanethics/forms

23 January 2014

HREC/REF: 046/2014

Dr I Okpechi
Division of Nephrology & Hypertension
E-13 Renal Unit
NGSH

Dear Dr Okpechi

Project Title: **EPIDEMIOLOGY AND CLINICAL OUTCOMES OF PATIENTS IDENTIFIED WITH IDIOPATHIC MEMBRANOUS GLOMERULONEPHRITIS(MGN) AT GROOTE SCHUUR HOSPITAL OVER A 10 YEAR PERIOD**

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee for review.

It is a pleasure to inform you that the HREC has **formally approved** the above mentioned study.

Approval is granted for one year until the 30 January 2015.

Please submit a progress form, using the standardised Annual Report Form, if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.

We acknowledge that the following student:- Dr O Ameh is also involved in this study.

Please note that the on-going ethical conduct of the study remains the responsibility of the principal investigator

Please quote the HREC REF in all your correspondence.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, HSF HUMAN ETHICS

Hrec/ref:046/2014

Appendix 3: Data Capture Sheet

EPIDEMIOLOGY AND CLINICAL OUTCOMES OF PATIENTS IDENTIFIED WITH IDIOPATHIC MEMBRANOUS GLOMERULONEPHRITIS (IMGN) AT GROOTE SCHUUR HOSPITAL OVER A TEN YEAR PERIOD (1ST JANUARY, 2003- 31ST DECEMBER, 2013)

DATA CAPTURE SHEET

SECTION I: DEMOGRAPHIC AND BASIC INFORMATION

Patient's Initials_____

ID code: _____ Serial Number: _____ Date of Birth: _____ (DD/MM/YY)

Gender: Male ☐ Female ☐

Race: Black ☐ Non-Black ☐

Marital status: Single ☐ Married ☐ Divorced ☐ Widow (-er) ☐

SECTION II: CLINICAL CHARACTERISTICS

Date of Biopsy _____ (DD/MM/YY) Date of last clinic visit_____ (DD/MM/YY)

Hypertensive: Yes / No (tick appropriate response)

- If Yes, duration (years):_____

Complications of disease: Yes / No (tick appropriate response)

- If Yes, DVT_____ Pulmonary embolism _____

Complications of treatment: Yes / No (tick appropriate response)

- If Yes, leucopenia _____ sepsis _____

Medications

	YES	Date commenced	NO
ACEi/ AARB			
Statins			
Immunosuppression			

Blood pressure

	Biopsy	Last follow-up	6 months	12 Months	24 Months	60 Months	120 Months
Systolic BP							
Diastolic BP							

SECTION III: HISTOLOGIC FINDINGS

No of glomeruli_____ No sclerosed_____

Interstitial fibrosis: None ☐ Mild ☐ Moderate ☐ Severe ☐

Electron microscopy grading: I / II /III / IV (circle appropriate grade)

Predominant immunohistochemistry findings: IgG ☐ C3 ☐ IgM ☐ IgA ☐

SECTION IV: CLINICAL CHEMISTRY

	Biopsy	Last follow-up	6 months	12 Months	24 Months	60 Months	120 Months
Albumin							
Cholesterol							
Serum Creatinine							
UPCR							
WCC							

SECTION V: IMMUNOSUPPRESSION CHART

Use of immunosuppression: **YES / NO** (tick appropriate)

	Start date (dd/mm/yy)	Dose per cycle*	Route (IV/PO)	Stop date (dd/mm/yy)	No of cycles
Methyl-Prednisone					
Prednisone					
Cyclophosphamide					

*alternating cycles of cyclophosphamide and corticosteroid

Other Medications

ACEi ☐ **ARB** ☐ **Statin** ☐ **(tick appropriate box if YES)**