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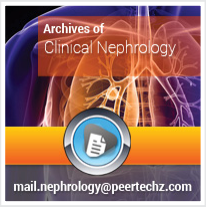

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Case Report

Steroid Monotherapy for the Treatment for Pure Membranous Lupus Nephritis: A Case Series of 5 Patients and Review of the Literature

Abstract

Introduction: The benefit of combination immunosuppression versus steroid monotherapy in pure membranous lupus nephritis (MLN) remains unclear. Steroid monotherapy could potentially reduce exposure to excessive immunosuppression in patients achieving remission with this strategy. The aim of this study was to define patient characteristics and outcomes in MLN treated with steroid monotherapy.

Method: A retrospective, observational study identified all biopsy-proven pure MLN cases followed since 1990 in a single center. Demographic, clinical and histological data were gathered for patients treated with daily steroid monotherapy. The primary outcome of interest was the reduction in proteinuria, reported as complete remission (CR), partial remission (PR) or no response.

Results: We identified 5 patients who received steroid monotherapy for pure MLN. The patients were 80% female with preserved renal function and little, if any, evidence of chronic interstitial fibrosis on biopsy. The mean follow-up period was 79.4±57.6 months. All cases achieved a clinical remission (CR in two patients and PR in 3 patients). The three patients who achieved only partial remission had a relapse during follow-up, which were successfully treated by addition of further immunosuppression, whereas the two patients who achieved CR did not experience a relapse. The mean estimated GFR was similar at baseline and the latest follow-up, 117±20.7ml/min/1.73m2 vs 111±11.3ml/min/1.73m2, respectively (p=0.61).

Conclusion: Daily steroid monotherapy may be an appropriate first-line treatment for pure MLN. Larger, prospective, trials are needed to validate this strategy and identify those patients who are most likely to benefit.

Abbreviations

MLN: Membranous Lupus Nephritis; GFR: Glomerular Filtration Rate; CR: Complete Remission; PR: Partial Remission; LN: Lupus Nephritis; SLE: Systemic Lupus Erythematosus; ESKD: Endstage Kidney Disease; ISN/RPS: International Society Of Nephrology/Renal Pathology Society; CKD-EPI: Chronic Kidney Disease Epidemiological Collaboration; C3: Complement Factor 3; C4: Complement Factor 4; Upcr: Urine Protein Creatinine Ratio; AZA: Azathioprine; MMF: Mycophenolate Mofetil; Csa: Cyclosporine A; IVCY: Intravenous Cyclophosphamide

Introduction

Membranous lupus nephritis (MLN) accounts for approximately 10-20% of lupus nephritis (LN) [1]. The clinical presentation of MLN is variable, ranging from isolated sub-nephrotic proteinuria to nephrotic syndrome with reduced glomerular filtration rate (GFR), with or without extra-renal manifestations of SLE, positive lupus serology or hypocomplementemia [2]. Although associated with a better prognosis than proliferative LN, MLN can lead to significant morbidity, including thrombosis and infection associated with the nephrotic syndrome, transition to a proliferative LN in approximately one-third of patients and progression to end-stage kidney disease (ESKD) in approximately 10% of patients after 10 years [3].

All patients with LN should receive treatment with hydroxychloroquine, unless there is a contraindication, and renin-angiotensin-aldosterone system blockade should be introduced if there is proteinuria >0.5g/day and/or if anti-hypertensive medication is required to achieve blood

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pressure control <130/80mmHg [4]. Immunosuppression is typically indicated for persistent nephrotic-range proteinuria or declining renal function as, unlike primary membranous nephropathy, the likelihood of spontaneous remission in MLN is low [5,6]. Steroid monotherapy has been associated with high remission rates and excellent renal survival [7]. However, combination immunotherapy may be superior in inducing remission in MLN with nephrotic proteinuria [8]. There is presently no consensus on which patients may be suitable for a trial of steroid monotherapy in the first instance. Clinical practice guidelines have highlighted the need for further investigation into the role of steroid monotherapy in LN [9]. In this study, we report the clinical and histological characteristics and clinical outcomes of MLN treated with steroid monotherapy in a single tertiary referral centre and review the available clinical literature on steroid monotherapy in pure MLN.

Methods

Patient selection and treatment

A retrospective, observational study in a single tertiary centre identified patients from January 1990 until June 2014 with a biopsy-proven diagnosis of pure MLN (ISN/RPS Class V lupus nephritis). Cases with biopsy-proven mixed proliferative and membranous LN were not included. Other eligibility criteria included age ≥17 years old at the time of initiation of treatment, at least 2 years of follow-up and baseline proteinuria exceeding 2g/day (or urine protein/creatinine ratio, uPCR, ≥200mg/mmol). Demographic and clinical data collected from the electronic medical record included age, gender, ethnicity, duration of SLE diagnosis, presence of extra-renal SLE manifestations, medications, serum creatinine, CKD-EPI eGFR, serum albumin, C3 level (reference range 0.8-1.8g/L), C4 level (reference range 0.1-0.5g/L), anti-dsDNA antibody level (<35iu/ml considered negative), 24-hour urinary protein excretion and/or spot urine protein/creatinine ratio (uPCR). The renal biopsy histology was examined from the time of initial diagnosis of pure MLN.

To be considered as a steroid monotherapy-treated case, the patient must not have received non-corticosteroid immunosuppression (such as mycophenolate mofetil (MMF), azathioprine (AZA), cyclosporine (CsA), tacrolimus or cyclophosphamide) for at least 3 months prior to MLN treatment. Corticosteroid dosing in this cohort consisted of daily oral prednisone at 0.5-1mg/kg for 4-6 weeks, tapered over 6-12months depending on the clinical course. The use of anti-malarial medications was permitted. The treatment regimen was directed by the preference of patient's treating nephrologist. Local ethics board approval was obtained prior to data collection.

Outcome measures

The primary outcome measure of interest was renal remission as defined by a complete remission (CR), partial remission (PR) or no response based on serial proteinuria measurements. CR was defined as a reduction in proteinuria to <0.3g/24h (or uPCR<30mg/mmol), sustained over three months. PR was defined as a decline in proteinuria <3g/24h but >0.3g/24h (or uPCR<300mg/mmol and >30mg/mmol) plus ≥50% reduction from the initial level, sustained over three months. Non-response was failure to achieve either CR or PR. For patients with sub-nephrotic proteinuria, CR was defined as above and PR as ≥50% reduction in proteinuria sustained over 3 months. Secondary outcome measures were eGFR at the latest follow-up and time to first relapse for those achieving remission. The eGFR was compared from the baseline value to the last available follow-up. In nephrotic patients who achieved CR, a relapse is defined as recurrence of proteinuria of >3g/24 (uPCR >300mg/mmol). For those who achieved PR, a relapse was defined as recurrence of proteinuria of >3g/day and at least a 50% increase from the lowest sustained level of proteinuria achieved during PR. For patients with sub-nephrotic proteinuria at diagnosis who achieved CR or PR, a relapse episode could also be defined as recurrence of proteinuria of >2g/day (uPCR>200mg/mmol). Continuous variables were expressed as mean values (±SD) and compared using Student's t-test. Categorical variables were expressed as absolute numbers or percentage of the total group. An alpha level of 0.05 was deemed statistically significant.

Result

Baseline demographic, clinical and treatment characteristics

Twenty-six patients with MLN were identified, with 12 patients then excluded (5 in paediatric care, 4 inadequate data, 2 proteinuria <2g/day, 1 declined immunosuppression). Of the eligible patients (n=14), five received steroid monotherapy and nine received combination therapy. The steroid monotherapy patients were predominantly female gender (80%), had a mean at SLE diagnosis of 25.6±19 years, a mean duration of SLE prior to MLN diagnosis of 85.6±90 months, a mean baseline serum albumin of 25.8±9.5g/L, baseline daily proteinuria of 3.49±1.3g and baseline eGFR of 117±11.3ml/min/1.73m^2 (Table 1). The proportions with a normal serum C3 level and a normal C4 level were both 60%. Anti-dsDNA antibodies were detectable in 80% of the patients, but were considered elevated in only half of these. Two of the five patients had sub-nephrotic proteinuria at baseline. Extra-renal SLE manifestations were present in 2 patients, consisting of skin rash, oral ulcers and arthralgia at the time of diagnosis of MLN in both patients. The mean initial prednisone dosage was 0.66±0.2mg/kg/day. Hydroxychloroquine and sustained use of renin-angiotensin system blockade from the outset of treatment was evident in only 1 of the patients.

Renal biopsy characteristics

The renal biopsy findings at the time of diagnosis of pure MLN were examined based on light microscopy, direct immunofluorescence and electron microscopy, and are summarized in table 2. Similar characteristics were noted across the five biopsy samples. There were no sclerosed glomeruli in any sample and only mild, if any, mesangial hyper-cellularity and/or increased mesangial matrix. The glomerular basement

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membrane thickness was normal in all samples, consistent with early stage membranous glomerulopathy. The renal parenchyma was well preserved, with little, if any, interstitial fibrosis and tubular atrophy reported. Visualized blood vessels were normal in all cases. The degree of podocyte foot-process effacement reported was variable, which likely reflected the particular glomerulus or glomeruli that were available for viewing.

Table 1: Baseline demographic, clinical and treatment characteristics of patients receiving steroid monotherapy for the treatment of pure MLN.

Case No	1	2	3	4	5
Gender	Female	Male	Female	Female	Female
Race	Af	Cau	As	As	As
Age at SLE diagnosis (years)	19	55	24	17	15
Duration of SLE* (months)	0	92	120	0	216
Extra-renal signs*	No	Yes	Yes	No	No
Serum Albumin (g/L)	18	40	24	17	30
eGFR (ml/min/1.73m^2)	150	104	125	101	105
Proteinuria (g/day)	5.1	2.1	2.48	3.2	4.6
C3 level (g/L)	1.08	0.99	0.49	1.13	0.5
C4 level (g/L)	0.16	0.1	0.05	0.11	0.06
Anti-dsDNA titre	20	0	100	101	22
SLEDAI score	9	17	21	11	11
Initial Prednisone Dose (mg/kg/day)	0.7	0.5	0.5	1.0	0.6
RAAS blockade	No	Yes	No	No	No
Anti-malarial agent	No	Yes	No	No	No

*At the time of pure MLN diagnosis.

Abbreviations: Af=African ancestry, Cau=Caucasian, As=Asian, eGFR=estimated glomerular filtration rate, C3=complement factor 3 level, C4=complement factor 4 level, dsDNA=double-stranded deoxynucleic acid, SLEDAI=Systemic lupus erythematosus disease activity index, RAAS=renin-angiotensin-aldosterone system.

Clinical outcomes

The mean duration of follow-up was 79.4±57.6 months. All five patients treated with steroid monotherapy achieved an initial remission (Table 3). The CR and PR rates were 40% and 60%, respectively. The mean time to CR was 7.5±6.7months and the mean time to PR was 5.6±3.2months. Of the two patients who had sub-nephrotic proteinuria at baseline, one achieved CR and the other achieved a PR. During follow-up of the five cases a relapse rate of 60% was observed, all in patients who achieved an initial partial remission. Both patients who achieved an initial complete remission remained relapse-free during follow-up. The time to relapse from the time of initial remission was 13.3±18.8 months. The three patients who experienced a relapse were successfully treated with additional immunosuppressive agents, achieving a lasting CR in 2 cases and PR in the other case for the remaining follow-up time. The mean eGFR at baseline and at the latest follow-up was similar, 117±20.7 ml/min/1.73m^2 vs 111±11.3 ml/min/1.73m^2, respectively (p=0.61). No patient required renal replacement therapy or hospitalization for an infection-related adverse event or acute kidney injury during follow-up.

Discussion

In this series of five patients with pure MLN receiving steroid monotherapy, a clinical remission was achieved in all cases. Both patients who achieved an initial complete remission with steroid monotherapy did not experience a

Table 2: Summary of renal histology findings in the five cases receiving steroid monotherapy for the treatment of pure MLN.

Case No	1	2	3	4	5
Light Microscopy	0 of 19 glomeruli sclerosed; Mild increase in mesangial cellularity; Minimal interstitial fibrosis without tubular atrophy; Normal blood vessels	0 of 12 glomeruli sclerosed; Mesangial cellularity and matrix normal; No interstitial fibrosis or tubular atrophy; Normal blood vessels	0 of 44 glomeruli sclerosed; Mild increase in mesangial matrix and cellularity; 5-10% interstitial fibrosis and tubular atrophy; Normal blood vessels	0 of 10 glomeruli sclerosed; Mild increase in mesangial matrix. No interstitial fibrosis; Normal blood vessels	0 of 13 glomeruli sclerosed; Mild increase in mesangial matrix and cellularity; No interstitial fibrosis or tubular atrophy; Normal blood vessels
Immunofluorescence	Diffuse, granular capillary staining for IgG 3+ IgA negative C3 3+ C1q negative Kappa 3+ Lambda 1-2+	Diffuse, granular capillary staining for IgG 3+ IgA 2-3+ IgM 1+ C3 3+ C1q 2-3+ Kappa 3+ Lambda 3+	Diffuse, granular capillary staining for IgG 3+ IgA negative IgM 1+ C3 3+ C1q 2-3+ Kappa 3+ Lambda 3+	Diffuse, granular capillary staining for IgG 3+ IgA 2+ IgM 2+ C3 negative	Diffuse, granular capillary staining for IgG 3+ IgA 2+ IgM 1+ C3 2+
Electron microscopy	Mesangium contains a few electron-dense immune deposits; Diffuse sub-epithelial deposits; GBM thickness normal; TRIs present; Diffuse podocyte effacement	Mesangial immune deposits, but no sub-endothelial deposits; Diffuse sub-epithelial deposits; GBM thickness normal; No TRIs present; Diffuse podocyte effacement (90%)	Mesangium expanded with electron-dense immune deposits; Diffuse sub-epithelial deposits; Rare sub-endothelial deposits, GBM thickness normal; No TRIs; Moderate (50%) podocyte effacement	Mesangium normal; GBM normal thickness; Many electron dense sub-epithelial deposits; No sub-endothelial deposits; No TRIs; No podocyte effacement evident (only 1 glomerulus available)	Rare mesangial and sub-endothelial immune deposits; GBM normal thickness; Many electron dense sub-epithelial deposits; No TRIs; Variable podocyte effacement from mild to diffuse (3 glomeruli available)

Abbreviations: GBM=glomerular basement membrane, TRI=tubulo-reticular inclusion.

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Table 3: Clinical Outcomes for the five cases receiving steroid monotherapy for the treatment of pure MLN.

Case No.	1	2	3	4	5
Follow-up (months)	34	92	26	170	75
CR	No	No	Yes	Yes	No
Time to CR (months)	-	-	12	3	-
PR*	Yes	Yes	-	-	Yes
Time to PR (months)	2	7	-	-	8
Relapse	Yes	Yes	No	No	Yes
Time to Relapse (months)	4	1	-	-	35
Additional Immunosuppression added**	CSA + MMF	AZA	-	-	AZA
Subsequent Remission Achieved	CR	CR	-	-	PR
Time to Remission from Relapse	7	26	-	-	4
eGFR at last follow-up (ml/min/1.73m^2)	103	98	125	120	109

*reported for those who did not achieve a complete remission
**in addition to prednisone.

relapse during follow-up. However, there was a high risk of relapse noted during follow-up for those patients who initially achieved only a partial remission. Relapses were successfully managed by addition of immunosuppressive agents in addition to corticosteroids. The patients who were selected for steroid monotherapy had preserved renal function and similar renal histological characteristics demonstrating little, if any, chronic renal parenchymal damage. The use of RAAS blockade and anti-malarial agents was low in this cohort.

There is limited clinical literature examining the use of steroid monotherapy in pure MLN. A single, small, randomized-controlled trial has evaluated the treatment of pure MLN to date, comparing steroid monotherapy, CsA (plus steroid) and low-dose intravenous cyclophosphamide (IVCY) (plus steroid) [10]. The steroid monotherapy arm (n=15) had a median age of 40 years (range 20-58), median duration of SLE of 11.5months (range 3-120), daily proteinuria 5.7g (range 2.8-10.6) and the majority had normal serum complement levels and normal anti-dsDNA antibody titres. The monotherapy group performed poorly, achieving a 12-month cumulative probability of remission of 27% compared to 60% with IVCY and 83% with CsA. However, prednisone dosing was only on alternating days, which is not reflective of practice in many centers. Radrakrishnan et al. reported that MMF and IVCY had comparable 6-month remission rates in a pooled analysis of pure MLN patients from two randomized controlled trials [11]. However, both arms also received corticosteroid therapy (0.75-1mg/kg/day) and it is conceivable that there was no difference in the outcomes between the MMF and IVCY groups due to the corticosteroids in each group being the primary active therapeutic agent. Pasquali et al. reported similar remission rates in patients with MLN treated with both corticosteroid monotherapy or combination therapy [12]. In a retrospective cohort of 19 patients, Moroni et al. found that combination immunosuppression appeared more favourable for renal function preservation and a lower relapse rate compared to steroid monotherapy [13].

A systematic review and metanalysis of MLN treatment has suggested that combination therapy is superior to steroid monotherapy, achieving a higher response rate of 81% vs 60%, respectively [8]. The optimal agent to use in addition to steroids was unclear. Subsequent to this report, Bitencourt-Dias et al. compared daily prednisone (n=29) to combination therapy (n=24), using cyclophosphamide or AZA for 6 months, in patients with MLN, mostly with nephrotic proteinuria. The steroid monotherapy group had similar characteristics to our cohort, predominantly young, female patients with preserved renal function and proteinuria <5g/day. Prednisone monotherapy achieved a high remission rate after 6-months, which was comparable with combined therapy, 100% vs 70%, respectively [7]. Renal survival after 8 years was similar between the steroid and combination groups, 86.2% vs 75% respectively. The rate of renal flares was high and similar to our findings, 51.7% vs 62.5% in the steroid monotherapy group and combination groups, respectively. Baseline renal histological characteristics were not compared between the groups.

Infection-related mortality remains high in SLE cohorts [14,15]. Hospitalization for serious infections has increased substantially, now estimated to be 12 times higher than in patients without SLE in one national population-based study [16]. Patients with SLE may carry an intrinsically increased susceptibility for infection related to immune dysfunction, which is then further augmented by immunosuppression [17,18]. There is a complex interplay among infection, autoimmunity and immunosuppression in SLE, with the suggestion that immunosuppression may not be the dominant risk factor for infection in all cases [18,19]. However, most would view therapeutic strategies to minimize exposure to immunosuppression, particularly in young patients potentially faced with many years of cumulative treatment, as advisable. Conversely, as persistent proteinuria in LN is a major predictor of progressive chronic kidney disease, those not responding to a less potent regimen should have their immunosuppression intensified [20]. Patients who achieved remission with steroid monotherapy appear to do so within several months, hence, additional immunosuppression could be considered if there is no significant response within 6-12months. The current study, like others, is limited most notably by its small sample size and retrospective, observational design.

Conclusion

Steroid monotherapy may be an effective treatment in MLN, potentially avoiding the need for excessive immunosuppression for some patients. Ultimately, the decision to initiate steroid monotherapy in a patient with MLN will likely depend on their clinical presentation. Our data suggests that, if effective, these patients are likely to enter remission within several months and this could be used to guide the addition of further immunosuppression. The rate of relapse appears high with steroid monotherapy, which is consistent with previously reported cohorts. The present series is limited by design and small sample size, but warrants further investigation into the role of steroid monotherapy in MLN. Future prospective and larger studies should aim to identify which patients are suitable for a trial of steroid monotherapy and which patients are likely to have a favourable response.

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