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It is Necessary to use High Doses of Steroids in the Therapy of Membranous Nephropathy?

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Abstract

Idiopathic membranous nephropathy (IMN) has a variable course with frequent spontaneous remission, therefore some authors recommend only non-specific therapy. But in the cases with nephrotic syndrome, the risk of kidney failure is greater in the untreated patients than those who are treated. Various therapeutic schemes proposed in recent years have shown favorable results as a famous Ponticelli regimen, but almost all included the use of immunosuppressants. Although used at low doses, immunosuppressants have the risk of causing long-range tumors over the course of many years. The monotherapy with steroids is not recommended in this nephropathy. We have put in place a therapeutic protocol by usingonly methylprednisolone at low doses to see if it was possible to get a remission of nephrotic syndrome, in order to avoide important side effects. We have treated eleven patients with idiopathic adult membranous nephropathy documented so by renal biopsy and nephrotic syndrome. It was observed a complete remission in 7 patients and a partial remission patients. in 3patients. Onlyone patient did not respond. The follow-up was 17.5 months (3-48 months). In 5 patients total remission persisted after 28.8 months on average (12-48 months). In 2 patients with complete remission and 3 with partial remission, a recurrence of nephrotic syndrome occurred after an average of 6.2 months (3-12 months). These results seem interesting, but before drawing any conclusion, it will be necessary to extend the cases and the follow-up procedure.

Introduction

Idiopathic Membrane Nephropathy (IMN) is one of the most frequent adult glomerulonephritis frequently associated to the clinical picture of nephrotic syndrome. Its evolution is variable. IMG seems a relatively benign disease. A review of 11 reports of the natural history of the disease demonstrated a 10-year renal survival within the relatively tight band of 70% to 90%. A more current pooled analysis of 32 studies estimated survival between 65% and 75% at 10 years and 60% at 15 years (1). Among the risk for an unfavorable course are older age at onset, male sex, very heavy proteinuria (greater than 10 g/d), sustained hypertension, impaired renal function, and significant chronic tubulointerstitial lesions in the initial renal biopsy. Patients lacking these prognostic features usually do quitewell with a highly likelihood of spontaneous complete or partial remissions and stablerenal function (2) Some authors proposed not to treat these patiens. (3), but in presence of evident nephrotic syndrome the majority of authors have demonstrated that the treated patients have a better prognosis than the untreated ones (4-5-6). Once a complete remission has occurred, whether spontaneous or induced, the long-term evolution of the IMG is favorable. (7). Over the years, various therapeutic schemes have been suggested starting from the randomized trials of Ponticelli (8-9) which has proposed alternate cycles of steroids and chlorambucil or cyclophosphamide with positive results and few side effects. Other authors(10-11) reported positive results with association of steroids to Mycophenolate, Tacrolimus, Ciclosporin, and recently Rituximab. The aim of this paper is to report our experience with a scheme that uses Methylprednisolone alone in patients with nephrotic syndrome and bioptic diagnosis of membranous nephropathy.

Materials and Methods

We conducted a retrospective study on 11 adult patients with nephrotic syndrome (proteinuria> 3.5 g / day) and glomerular filtration (Cockroft formula) > 30 ml / min, all subjected to renal biopsy with membranous nephropathy diagnosis. (Tab.1). The patients were 7 males and 4 females. The average age was 39,6 years (24-59). The mean creatinine was 1.26 mg / dl (0.7-2.4), glomerular filtration was 69.8 ml / min (33-86). Hypertension was present in 9 cases. At the early stages of the study all the patients had high proteinuria (on average 9.2 g / day (6-16), edema, hypoproteinemia and hypercholesterolemia. The nephrotic syndrome was primitive, brought in full well being, with no associated pathologies. Only in one case there were recurrent tonsillitis and in the other case there was Hashimoto's thyroiditis associated. The biopsy showed a picture of membranous nephropathy at stage 2 in seven cases and at stage 3 in four cases. All patients were treated with a protocol we created based on previous experiences of nephrotic syndromes treated with positive outcome, but that had been not subjected to renal biopsy. Our protocol included: induction therapy with Methylprednisolone bolus iv 500 mg x 3 days if glomerular filtration was > 50 ml / min, 250 mg x 3 days if < 50 ml/min, followed per os 0.5 mg / kg for 6 days on 7 at week for a month and after 0.5 mg / kg at alternate days. The patients were examined every month. At each visit, plasma creatinine concentration and 24-h urinary protein excretion rates were examined and the patients were questioned about symptoms and possible side effects of therapy. The duration was variable and was determined based on the proteinuria values. In case of complete persistent remission (proteinuria <0.3 g / day or negative to dipstick) after 2 examinations performed once a month for a period of two months, steroid therapy was suspended slowly within 2 weeks time. In patients with partial response (protein excretion between 0.3 and 1 g / day), the treatment was continued for a period of 12 months. All patients, including normotensive patients, were treated with ACEI or ARB that continued after steroid suspension. We excluded patients with diabetes, glomerular filtration <30 ml / min, age <15 or > 70 years and patients who had received previous treatment with immunosuppressive drugs.

Tab1 Ourcasistic. Hyp: *hypertension.-Bolus iv of Methylprednisolone. Lenght of therapy months -CR: complete remission. PR: partialremission. W: worsened. Prot1 and Creat1:proteinuria and creatininemiaat the end of therapy. FU: follow-up after the end of steroid therapy.*

Patients	Sex	Age	Prot	Creat	Hyp	Therapy		Results	Prot1	Creat1	FU	Relapse
		years	g/die	mg/dl		Bolus	Lenght		g/die	mg/dl	months	
AB	M	50	10	1,0	+	500 mg	12	CR	0,1	0,9	36	No
CE	M	39	6,6	2,1	+	250	12	PR	1,5	1,3	3	Yes
ID	M	59	12	2,4	+	250	5	W	8,8	5,3	-	
KB	M	24	6,5	1,2	-	500	13	CR	0,3	1,0	5	Yes
MP	M	29	7,6	0,9	+	500	8	CR	0,2	0,9	3	Yes
AR	F	44	6,3	0,7	-	500	12	PR	0,7	0,8	12	Yes
LA	F	45	6,0	0.8	+	500	6	CR	0,3	0,6	12	No
XK	F	29	10	0.9	-	500	10	CR	0,1	0.8	36	No
OC	F	45	15	1.4	+	500	7	CR	0.2	1.3	12	No
AS	M	41	8	1.2	+	500	12	CR	0.1	1.1	48	No
AV	M	28	9.2	1.3	+	500	12	PR	1.6	1.4	8	Yes

Results

We examined our outpatient clinic and selected 11 patients with Idiopathic Membranous Nephropathy withNephrotic Syndrome documented by renal biopsy. (Tab.1). As outlined in our protocol, 9 patients with glomerular filtration> 50 ml / min were treated at the beginning, with 500 mg iv for 3 day of Methylprednisolone 2 with glomerular filtrate <50 ml / min with 250 mgboliiv for 3 days, followed per os as a schema. The duration of the Treatment averaged 9,4 months, with a variation between 5 to 14 months. No patient showed any side effects that would induce them to the suspension of the therapy. In 7 patients we observed a complete remission while in 3 patients we observed a partial remission. Only one case resulted in a negative result. It was what initially showed the highest creatinine (2.4 mg / dl) and the therapy was suspended after 5 months due to an evident increase of creatinine and high proteinuria persistence. In other patients, mean creatinine did not show any significant differences compared to baseline values. The follow-up was 17.5 months (3-48 months). In 5patients total remission persisted after for a period of 28.8 months on average(12-48 months). In 2 patients with complete remission and 3 with partial remission, a recurrence of nephrotic syndrome occurred after an average of 6.2 months (3 to 12 months). The response to therapy was independent of histology, the extent of proteinuria and the presence of hypertension. The presence of high creatinine had affected the only negative response case.

Discussion

Idiopathic membranous nephropathy (IMN) is the most common form of nephrotic syndrome in adults. The disease shows a benign or indolent course in the majority of patients, with a rate of spontaneous complete or partial remission of nephrotic syndrome as high as 30% or more.(3). Despite this, 30% to 40% of patients progress toward end-stage kidney disease within 5 to 15 years (12). There was no clear evidence to support the use of either corticosteroid or alkylating agent monotherapy.(11-12) Also KDigo guidline recommends the non useof cortisone monotherapy in this nephropathy (13) A combined alkylating agent and corticosteroid regimen had short- and long-term benefits on adult IMN with nephrotic syndrome.(14-15). Among alkylating agents, cyclophosphamide was safer than chlorambucil (9). Therapeutic schemes involving the use of high doses of cortisone plus immunosuppressant for prolonged periods were significantly associated with more withdrawals or hospitalisations (12). Cyclosporine has beneficial effects but it causes frequent relapses after suspension (16) The studies related to tacrolimus, mycophenolate mofetil, adrenocorticotropic hormone, azathioprine, are still too sparse to enable the drawing to final conclusions.(17) A Long-term follow-up for a period of more than 10 years will be required to establish the magnitude of the oncogenic potential of immunosuppressive therapy. (18-19). ACE inhibitors or ARB may be useful in patients without nephrotic syndrome and can support the steroids and immunosuppressive therapy in nephrotic syndrome (20).

The data we provide are retrospective and limited to a small number of patients, but we believe that even with its limits, our experience may be interesting because we use Methylprednisolone alone without immunosuppressors. Ponticelli (21) in a controlled trial compared a group of patients with IDM treated with methylprednisolone plus chlorambucil for 6 months against a group treated with Methylprednisolone with bolus at 1st, 3rd and 5th month and prednisolone per os 0.4 mg / kg on alternate days for 6 months. In the first group, a frequency of early remission was observed, but over time the differences were no longer significant. Despite the poor opinions on the use of steroids in monotherapy in this nephropathy (13), we have proposed to evaluate a therapeutic scheme that provides, after induction with bolus of metylprednisolone ranging from 500 mg to 250 mg according to creatinine, low-medium steroid doses with a suspension one day a week the 1st month and then on alternate days in the following months with a non-fixed duration, based on the proteinuria response. Our final intention was the retraction of outmost results associated with minimal side effects. The results appear to be encouraging: out of a number of 11 patients there were 7 patients with total remission, 3 patients with partial remission after an average of 9,4 months steroid therapy. Only

one patient did not respond to the therapy. It should be noted that complete remission of proteinuria is a strong predictor of long-term favorable outcome in patients with idiopathic membranous nephropathy (7).

After stopping steroid therapy, 5 patients reported a recurrence of nephrotic syndrome that affected all those who had had partial remission and 2 of those with complete remission. The frequency of relapses was similar to those reported by other authors, who had used steroids plus immunosuppressants (22-23) In the relapsing patients, we used steroid therapy plus an immunosuppressors.

In conclusion, the use of low-medium doses of methylprednisolone in the Membranous nephropathy favored the remission of nephrotic syndrome without obvious side effects. These preliminary data will have to be confirmed by the extension of casistic and follow-up.

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