

The “Ponticelli” Therapy in the Idiopathic Membranous Nephropathy: an Italian invention

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Introduction

Idiopathic Membranous Nephropathy (IMN) is one of the most frequent adult glomerulonephritis often associated to the clinical picture of nephrotic syndrome. In the IMN the antigens are probably located at the base of podocytes, and the glomerular lesions occur by the local formation of immune complexes, with consequent activation of complement and inflammation triggered by the membrane attack complex C5b-9 [1]. Its evolution is variable. The IMN 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 [2]. 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 quite well with a highly likelihood of spontaneous complete or partial remissions and stable renal function [3].

Some authors proposed not to treat these patients. [4], 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 [5,6]. Once a complete remission has occurred, whether spontaneous or induced, the long-term evolution of the IMN is favorable [7].

Various steroid and immunosuppressant therapies had been proposed, but with controversial results. There was no good evidence in favor of therapies based on corticosteroids alone. Cyclophosphamide and chlorambucil may increase the probability of remission, but the prolonged use of these agents may cause dangerous adverse effects [8].

In 1984 the most innovative therapy of membranous nephropathy was proposed by Milan nephrologist Claudio Ponticelli [9]. I participated, together with 5 other Italian nephrological centers, in the study he invented. The

scheme has a duration of 6 months and provides alternate months with bolus steroids of 1 g /day for 3 days, then orally at 0.5 mg/kg/day for 27 days, alternating with Chlorambucil 0,2 mg/kg/day for 30 days. The study was carried out in 81 patients with nephrotic syndrome and biopsy diagnosis of membranous nephropathy, 49 of whom were treated and 39 as a control group without specific therapy. In the event of recurrence or persistence of nephrotic syndrome, the cycle was repeated for another time. The results with a follow-up of 31,4+-18,2 months were extremely favorable: in the 32 patients who completed the therapeutic course, at the end of the follow-up, 12 were in complete remission (proteinuria < 0,2 g/die), 11 in partial remission (proteinuria between 0,2 and 2 g/die), 1 were unchanged (proteinuria > 2 g/die) and none were worse (plasma creatinine > 50% of the base-line levels). Among the 30 controls, 2 patients were in complete remission, 7 in partial remission, 13 were unchanged and 1 were worse. There were a significantly difference between the patients in remission (complete or partial) in the treated group (72%) than in the control group (30%) ($P<0,001$). Side effects were rare and mild: gastric pain in 2 patients and a transient increased level of serum transaminase in one patient were observed during the Chlorambucil cycle, but none of these patients had to stop the therapy.

In 1989 we published the data after an average follow-up of 5 years [10]. In the treated group 71% of patients were in remission against 17% of the untreated group and in the first group 10% had an increase in creatininemia against 44% of the untreated. The side effects were modest and only 4 patients did not complete the therapeutic scheme for gastric intolerance. This work had a worldwide resonance and the results were confirmed by other authors [3-11] so much that all over the world this therapy has been called “Ponticelli scheme” and adopted in many countries.

In 1992 we published the results of a new trial [12] comparing 45 patients treated with the previous scheme versus 47 patients treated with Methylprednisolone alone for 6 months. Here too the conclusions were in favor of the Ponticelli scheme.

In 1995 new work with 10-year follow-up data confirming the favorable effects of therapy, even in the long term [13]. In 1998 the results of a new trial arrived where we included cyclophosphamide in addition to methylprednisolone in the control group [14]. The conclusions were that both treatments were effective in promoting remission and preserving kidney function.

Since then, new therapeutic schemes with new drugs have been proposed for this nephropathy. Various authors [15-17] reported positive results with association of steroids to Mycophenolate, Tacrolimus, Ciclosporin, and recently Rituximab, but no one has

shown superior results to Ponticelli therapy which is still used in the world [18,19].

I had the honor of participating in the birth and development of this therapy and my name is present in all the works of the group. These works are continually cited in international literature and the USA website Academia pointed out to me that my name was mentioned in 226 international publications. Now that I am retired, I want to thank my friend Ponticelli (Figure 1) for giving me the opportunity to participate in the experiment he invented.



Figure 1: Claudio Ponticelli and Mauro Sasdelli in Tirana with Myftay Barbullushi, director of the Albanian school of Nephrology and nephrology graduate students (2019)

In conclusion, I am proud to have made my contribution to improving the therapy of insidious and subtle nephropathy and my name will remain in the history of Nephrology.

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