

Journal of Nephrologist



The use of modified Ponticelli regimens for primary membranous nephropathy

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ARTICLE INFO

Article type:
Editorial

Article history:
Received: 26 September 2019
Accepted: 10 October 2019
Published online: 18 October 2019

Keywords:
Immunosuppression, Modified Ponticelli, Primary membranous nephropathy

Implication for health policy/practice/research/medical education:

Given the comparable efficacy of the modified-‘modified Ponticelli’ regimens using lower doses of cyclophosphamide and corticosteroids, respectively, and cognizant of the natural history of primary membranous nephropathy (MN), every effort to mitigate the deleterious adverse effects of immunosuppression, while still not losing therapeutic efficacy in the management of primary MN, must continue to be encouraged.

Please cite this paper as: Onuigbo MAC. The use of modified Ponticelli regimens for primary membranous nephropathy. J Nephrologist. 2019;8(4):e34. DOI: 10.15171/jnp.2019.34.

Rao et al in a recent issue of this journal described their ten-year experience with the use of a modified- ‘modified Ponticelli’ regimen in the management of primary membranous nephropathy (MN) (1). Out of a total of 41 patients, 31 (76%) completed the six months’ immunosuppression treatment, 6 (15%) were lost to follow up while 4 (10%) discontinued therapy due to infections (1). Twenty-two (71%) responded to treatment, 8 (25%) achieved complete remission whereas 14 (45.2%) achieved partial remission (1). The most common complication was steroid-induced diabetes mellitus in 14 of 35 (40%) patients, infections in 3 of 35 (8.5%) patients and leucopenia in 3 of 35 (8.5%) patients (1). Nine (29%) patients relapsed during a mean follow up of 36 months (1). The authors concluded that the modified-‘modified Ponticelli’ regimen with lower-than standard intravenous steroids and cyclophosphamide was efficient in attaining remission in primary MN (1).

Over 30 years ago, Ponticelli and his group had demonstrated the efficacy of the combination of chlorambucil plus cyclophosphamide in the management of idiopathic MN (2-5). This represented the “Classical Ponticelli” regimen for primary MN. Subsequently, in 1998, Ponticelli and his group in a randomized open label study compared methylprednisolone (1g IV for 3

consecutive days followed by oral methylprednisolone, 0.4 mg/kg/d for 27 days) alternated every other month with either chlorambucil (0.2 mg/kg/d for 30 days) or cyclophosphamide (2.5 mg/kg/d for 30 days) for a total of six months (6). This study showed that both regimens were comparable in terms of remission rates and relapse rates (6). Thus was born the modified Ponticelli regimen. As a result, cyclophosphamide replaced chlorambucil as the alkylating drug of choice in the combination immunosuppression management of primary MN (1).

Nevertheless, there still remained significant concerns regarding the major adverse effects of such intense immunosuppression, especially given the natural history of primary MN. There is accumulating evidence that spontaneous remission of proteinuria occurs in 5%-30% of patients with primary MN at five years (7). Indeed, after a prolonged follow up of at least five years, 65% of 100 consecutive patients who received no immunosuppression were in complete or partial remission (7). It must be recognized that 16% of this cohort had progressed to end-stage renal disease (7). With the forgoing knowledge, there have been attempts over the years to reduce the intensity of immunosuppression for primary MN. Afterwards, Jha et al in 2007 demonstrated comparable efficacy of treating patients with primary MN using a lower dose of

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cyclophosphamide compared to that used by Ponticelli (2 mg/kg/d versus 2.5 mg/kg/d) (1,8).

Additional concerns still remained regarding the abrupt discontinuation of corticosteroids after the third steroid cycle that is usually the fifth month of the 6-months' Ponticelli regimen. Indeed, Ramachandran et al in 2015 studied 13 consecutive adult patients with idiopathic MN who had completed the modified Ponticelli regimen (9). The hypothalamic pituitary adrenal axis was evaluated using a low-dose adrenocorticotrophic hormone stimulation test, one month after completing the last course of steroid therapy (9). In this study, 3 of 13 (23%) patients had suppression of the hypothalamic pituitary adrenal axis.

We posit that given the comparable efficacy of the modified-'modified Ponticelli' regimens using lower doses of cyclophosphamide and corticosteroids, respectively, and cognizant of the natural history of primary MN, every effort to mitigate the deleterious adverse effects of immunosuppression, while still not losing therapeutic efficacy in the management of primary MN, must continue to be encouraged.

Author's contribution

MACO is the single author of this paper.

Conflicts of interest

The author declares no competing interests.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the author.

Funding/Support

None.

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