Chapter 8: Idiopathic membranoproliferative glomerulonephritis

Kidney International Supplements (2012) **2,** 198–199; doi:10.1038/kisup.2012.21

INTRODUCTION

This chapter makes treatment recommendations for MPGN believed to be of unknown cause (idiopathic MPGN) in adults and children. The cost implications for global application of this guideline are addressed in Chapter 2.

8.1: Evaluation of MPGN

8.1.1: Evaluate patients with the histological (light-microscopic) pattern of MPGN for underlying diseases before considering a specific treatment regimen (see Table 20). (*Not Graded*)

BACKGROUND

MPGN is a light-microscopic "pattern of injury" caused by many disorders (see Table 20).[304,305] Patients commonly present with nephrotic syndrome, hypertension, glomerular hematuria, and progressive kidney dysfunction.[304,305] Reduction in the serum concentration of complement components (C3 and/or C4) is commonly, but not uniformly, observed.[305,306]

MPGN can be further classified based on the extent and location of deposits of immunoglobulin and/or complement. The classification of MPGN according to ultrastructural appearances into MPGN type I, II, or III is commonly employed, but newer classification schema based on immunopathology are replacing this approach.[307,308] Type I MPGN is associated with subendothelial and mesangial electron-dense deposits containing immunoglobulin and/or C3,[305,309,310] and is often due to an underlying chronic hepatitis B or C infection (see Chapter 9); type II MPGN with electron dense intramembranous deposits containing numerous complement components, but not immunoglobulin[305,309] and is now known as "dense-deposit disease". It has a distinctive etiology based on inherited or acquired abnormalities of complement regulatory proteins.[305,311] Other rarer variants (type III MPGN) are also recognized based on abnormalities of the glomerular basement membrane and the location of electron-dense deposits. Immunopathological variants are recognized based on deposition of IgG and/or C3 component of complement in glomeruli. Those in which C3 is exclusively deposited are known as C3 GN.[305,307,308,311]

Treatment of MPGN is highly dependent on proper identification of underlying causes (see Table 20). In some patients C3 nephritic factor, an autoantibody to C3bBb, can be involved in the pathogenesis of type I, II, III, or C3 GN.[312,313]

Idiopathic MPGN is defined by exclusion of any other identifiable cause, most typically when the ultrastructural pattern is type I MPGN. Idiopathic type I MPGN is very uncommon in developed countries, but remains a relatively common, although diminishing, cause of nephrotic syndrome in developing countries, especially those with a high burden of endemic infectious diseases.[314]

RATIONALE

- Based on the heterogeneity of cause and pattern of histologic injury of MPGN, all patients with MPGN must be thoroughly evaluated for underlying diseases before being classified as idiopathic MPGN, and before any specific treatment decisions can be made.

8.2: Treatment of idiopathic MPGN

8.2.1: We suggest that adults or children with presumed idiopathic MPGN accompanied by nephrotic syndrome *AND* progressive decline of kidney function receive oral cyclophosphamide or MMF plus low-dose alternate-day or daily corticosteroids with initial therapy limited to less than 6 months. (*2D*)

RATIONALE

- There is very low–quality evidence to suggest the benefit of an immunosuppressive agent plus corticosteroids in the treatment of idiopathic (type I) MPGN with nephrotic syndrome and/or deteriorating kidney function.

MPGN is identified by exclusion of all other known causes of the MPGN pattern on kidney biopsy. When there is a secondary MPGN, i.e., a defined cause for the MPGN pattern (see Table 20), treatment should be directed against that cause. A review of the evidence for the management of each of those conditions enumerated in Table 20 is outside the scope of this guideline. This section will consider only those patients who *do not* have any recognized underlying cause or pathobiological mechanism for the MPGN lesion. Most of these patients will have the type I pattern by electron microscopy.

Many of the early reports of treatment of "idiopathic" MPGN likely inadvertently included cases of secondary MPGN. Therefore, the results of these studies must now be

Table 20 | Underlying conditions associated with a membranoproliferative pattern of GN

Chronic infections (especially hepatitis C)
Autoimmune diseases (especially LN)
Monoclonal gammopathies (especially light-chain deposition disease and monoclonal IgG disease)
Complement dysregulation (especially complement factor H deficiency)
Chronic and healed thrombotic microangiopathies

GN, glomerulonephritis; LN, lupus nephritis.

interpreted with great caution given today's knowledge regarding immunopathogenesis.[304,305,307,308] Truly "idiopathic" MPGN is now a very uncommon condition, except in certain developing countries with a high endemic burden of infections. The few RCTs of treatment of idiopathic MPGN in children and adults have given inconsistent and largely inconclusive results.[304,305] Many of the reported trials have weak experimental design or are underpowered, and thus the evidence base underlying the recommendations for treatment of "idiopathic" MPGN is very weak. Early claims of benefit for a combination of aspirin and dipyridamole for adults with idiopathic MPGN were later rejected[315,316] and benefits of "antiplatelet" therapy in "idiopathic" MPGN remain in doubt.[317,318]

The benefit of long-term alternate-day corticosteroid therapy for "idiopathic" MPGN in children was suggested by observational studies and a single RCT, but the results were equivocal; there have been no subsequent confirmatory RCTs.[319–322]

The benefits of immunosuppressive therapy (cyclophosphamide or MMF) often combined with high-dose i.v. or oral steroids have never been demonstrated in RCTs. However, small, observational studies with short-term follow-up have suggested a benefit, mostly in subjects with a rapidly progressive course, often associated with extensive crescents, or in those with progressive kidney disease with persistence of severe nephrotic syndrome.[145,317,323–329] Publication bias might be operative in these reports. Progressive renal failure remains the only indication for immunosuppressive treatment, but the overall evidence for efficacy and safety is weak. See Chapters 13 and 14 for discussion of treatment of those cases of MPGN with superimposed extensive crescentic lesions and rapidly progressive renal failure.

RESEARCH RECOMMENDATION

- An RCT is needed to test corticosteroids in combination with an immunosuppressive agent such as cyclophosphamide, MMF, or rituximab in "idiopathic" MPGN with nephrotic syndrome in adults and children.

SUPPLEMENTARY MATERIAL

Supplementary Table 35: Evidence profile of RCTs examining alternate-day prednisone treatment vs. control in adults and children with MPGN.

Supplementary Table 36: Summary table of studies examining alternate-day prednisone treatment vs. control in patients with MPGN (categorical outcomes).

Supplementary Table 37: Summary table of studies examining alternate-day prednisone treatment vs. control in patients with MPGN (continuous outcomes).

Supplementary Table 38: Summary table of studies examining dipyridamole plus aspirin treatment vs. placebo in patients with MPGN (categorical outcomes).

Supplementary Table 39: Summary table of studies examining dipyridamole plus aspirin treatment vs. placebo in patients with MPGN (continuous outcomes).

Supplementary Table 40: Summary table of study examining warfarin plus dipyridamole treatment vs. control in patients with MPGN (categorical outcomes).

Supplementary Table 41: Summary table of study examining warfarin plus dipyridamole treatment vs. control in patients with MPGN (continuous outcomes).

Supplementary material is linked to the online version of the paper at http://www.kdigo.org/clinical_practice_guidelines/GN.php