

Idiopathic membranous nephropathy: use of other therapies

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GUIDELINES

No recommendations possible based on Level I or II evidence

SUGGESTIONS FOR CLINICAL CARE

(Suggestions are based on Level III and IV evidence)

- While there have been mixed reports of success with a number of agents, further evidence is required before they can be recommended as second line therapy in membranous glomerulonephritis (MGN).

Azathioprine

Studies in the treatment of idiopathic MGN have found mixed benefits from using azathioprine combined with corticosteroids over steroid alone.

- Baker et al (1998) demonstrated that the addition of oral azathioprine to a regimen of intravenous pulse methylprednisolone and oral prednisone could reverse or stabilize progressive kidney failure in patients with membranous nephropathy.

Most series have not shown any benefit (Brown et al 1998).

- In a small controlled trial, five patients with the nephrotic syndrome due to idiopathic MGN received azathioprine, 2.5 mg/kg/d, while four others received placebo. After 1 year of treatment there was no significant difference in creatinine clearance or 24-hour excretion of protein between the two groups (Western Canadian Glomerulonephritis Study Group, 1976).
- The Sheffield Kidney Institute reviewed 58 patients with idiopathic MGN and nephrotic-range proteinuria (Ahuja et al, 1999). Thirty-eight patients were treated with prednisolone (1 mg/kg/d) and azathioprine (2 mg/kg/d) for a median period of 26 months. Twenty patients received no specific treatment for MGN and served as a control group. Neither the level of proteinuria, the rate of renal decline nor the proportion of patients with deteriorating renal function differed significantly between the groups. In addition, adverse effects of immunosuppressive treatment were observed in 9 patients.

Immunoglobulin

Pooled intravenous immunoglobulin in a few small series has been shown to reduce proteinuria and stabilize renal function in patients with resistant nephrotic syndrome (Levy et al, 1999) [Level III evidence, single study, additional selected case series].

- Palla et al (1986) followed 9 patients with idiopathic MGN following treatment with pulse doses of IgG (0.4 g/kg body weight) for 3 consecutive days, repeated 3 times at 21-day intervals for 10 months. In 5 patients, a complete remission of proteinuria (daily proteinuria less than 0.2 g) was observed, and 3 patients showed partial remission (proteinuria 2 g/day). In responder patients, clinical and biological findings of the nephrotic syndrome disappeared and a statistically significant increase of creatinine clearance was observed.
- Yokoyama et al (1999) reviewed 86 patients with primary MGN for at least 5 years. They treated 30 of these patients with 1–3 short-term courses of low-dose intravenous immune globulin (5–10 g/day) [100–150 mg/kg/day] for 6 consecutive days. There was no difference in the long-term outcome in patients treated with intravenous immunoglobulin therapy compared with patients not receiving therapy with immunoglobulin. A subgroup of patients with ‘homogenous type MGN with electron microscopy findings of synchronous electron-dense deposits’ had earlier induction of remission.

Fludarabine

Fludadrabine has been reported to lead to remission in some patients with MGN (Level IV evidence, anedoctal reports).

- Treatment of refractory chronic lymphocytic leukaemia (CLL) with fludarabine, a purine nucleoside analogue, has been associated with remission of malignancy-associated MGN (Butty et al 1999).
- Boumpas et al (1999) treated 7 patients with refractory idiopathic membranous nephropathy with 6-monthly cycles of fludarabine. Although all patients developed significant lymphopenia, proteinuria decreased by > 50% in 5 of 7 patients (P = 0.11) and glomerular filtration rate (GFR) improved in all those with renal failure at baseline.

Mycophenolate mofetil

Mycophenolate appears to reduce proteinuria in some patients with resistant MGN (Level IV evidence, small case series, variable results).

- Zhao et al (2001) treated 18 patients with refractory MGN, 13 of whom achieved remission on 1.0–2.0 g/d for 3–6 months.
- Miller et al (2000) treated 16 nephrotic patients with MGN with mycophenolate mofetil. Fifteen patients had steroid-resistant disease; cytotoxic agents had failed in 6 patients and cyclosporin therapy had failed in 5 patients. Six patients experienced a halving of proteinuria, which occurred after a mean duration of 6 months of therapy. Partial

remissions occurred in 2 patients. There were no significant changes in mean values for serum creatinine during the study.

- Briggs et al (1998) also described reductions in proteinuria and stabilising of creatine in 3 patients with MGN.
- Choi et al (2002) studied 17 patients with MGN including 15 with nephrotic range proteinuria and 6 with renal insufficiency. Indications for mycophenolate mofetil treatment were steroid- (11/17), cyclosporine- (4/17) or cytotoxic (1/17) dependency. After 5-12 months of follow-up, there was a 61.1% reduction in protein excretion. Two patients (13.3%), both of whom were nephrotic, achieved a complete remission; 8 patients (60%), all of whom were nephrotic, achieved a partial remission; and 2 patients (13.3%), including 1 nephrotic, had increased proteinuria. Eight of the 15 (53.3%) nephrotic patients improved to sub-nephrotic proteinuria with treatment. Two patients relapsed after mycophenolate mofetil was stopped, and they both responded to re-treatment. Three of 6 patients with renal insufficiency experienced substantial improvement in excretory renal function.
- Polenakovic et al (2003) gave mycophenolate mofetil 2 g/day for 9 months to 8 patients with stage III–IV idiopathic membranous nephropathy. Previous treatment had failed in 5 of 8 patients (three patients had received cyclosporin and steroids, one cyclosporin, steroids and cyclophosphamide and one an alternative use of steroids and chlorambucil). Proteinuria decreased significantly during the treatment ($P < 0.05$), from 4.4g/d at the start, to 2.0 g/day after 3 months, and 1.9 g/day after 6 months and 9 months. Renal function improved slightly, but not significantly ($P > 0.05$).

Monoclonal antibodies

Monoclonal antibodies against the cell surface antigen CD20 of B cells may reduce proteinuria in some patients with idiopathic MGN.

- Ruggenti et al (2003) followed 8 patients with idiopathic MGN and long-lasting persistent proteinuria, following an intravenous infusion of the anti-CD20 monoclonal antibody, rituximab. After 20 weeks of treatment, there was a 60% reduction in urinary proteinuria. At 12 months, proteinuria decreased to ≤ 0.5 g/24 h or ≤ 3.5 g/24 h in two and three patients, respectively. There was no significant loss of renal function in any patient.
- Eculizumab, a humanized monoclonal antibody that prevents the cleavage of human complement component C5 into its proinflammatory elements, did not appear to have any significant effect on proteinuria or renal function in patients with membranous nephropathy, although this Phase II study was not designed to test this outcome and the dose required for efficacy testing may not have been achieved (Appel et al 2002).

Background

Many patients with progressive kidney failure from MGN remain resistant to therapy with alkylating agents. There have been mixed reports of success with a number of agents. The objective of this guideline is to evaluate the available clinical evidence pertaining to the impact of specific interventions not covered in other guidelines on declining renal function in chronic kidney disease patients with idiopathic MGN. The potential utility of these agents in patients with secondary MGN is discussed in the guideline titled “Membranous nephropathy: role of cyclosporine therapy”.

Search strategy

Databases searched: MeSH terms and text words for Membranous Nephropathy were combined with MeSH terms and text words for azathioprine, immunoglobulin, fludarabine, mycophenolate mofetil and rituximab. This search was carried out in Medline (1966 to September Week 1, 2004). The Cochrane Renal Group Trials Register was also searched for trials in membranous nephropathy not indexed in Medline.

Date of search/es: 9 September 2004.

What is the evidence?

There have been no randomised controlled trials (RCTs) of these potential agents.

What do the other guidelines say?

Kidney Disease Outcomes Quality Initiative: No recommendation.

UK Renal Association: No recommendation.

Canadian Society of Nephrology: No evidence for the use of azathioprine (Level C).

European Best Practice Guidelines: No recommendation.

International Guidelines: No recommendation.

Implementation and audit

No recommendation.

Suggestions for future research

No recommendation.

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