Therapy of Membranous Nephropathy: What To Do After the After (Meta) Analyses

BELIEF: conviction of the truth . . . based on grounds insufficient to afford positive knowledge.
The American College Dictionary

The well-done meta-analysis by Imperiale et al. (1) helps confirm what my group has long believed, that immunosuppressive therapy with cytotoxic agents is effective in inducing remission of nephrotic syndrome in patients with idiopathic membranous nephropathy. Our belief is based on our rather substantial and well-discussed experience with idiopathic membranous nephropathy (over 140 patients evaluated at our institution for this disorder in the past 10 yr, many of whom received treatment directly or indirectly through our program). Thus, it was relatively easy for my group to become “believers” in cytotoxic therapy. However, what about the beliefs of nephrologists in solo practice or in small groups who may see only one or two of these patients annually? In addition, these nephrologists may have little opportunity to discuss with colleagues their experience in the treatment of membranous nephropathy and the voluminous and often conflicting literature on the subject. What are these nephrologists to believe about the use of cytotoxic therapy in membranous nephropathy? I respectfully suggest that they need only a small incentive to take the easier path, which is to not use cytotoxic therapy. Such an incentive was recently provided by work published in the New England Journal of Medicine by Schieppati et al. (2), stating that the outcome of idiopathic membranous nephropathy is so benign (although by 5 yr of follow-up, 16% had progressed to end-stage kidney failure) that it is not necessary to treat idiopathic membranous nephropathy (although this study did not examine the effects of treatment).

The meta-analysis by Imperiale et al. should cause more nephrologists to believe in immunosuppressive therapy in idiopathic membranous nephropathy. I suggest, however, that it is not sufficient to induce “belief” by meta-analyses or clever editorials. Rather, we need to know the truth with regard to the risks and benefits of cytotoxic therapy in idiopathic membranous nephropathy. Such “truth” can only come from a controlled, prospective, randomized, multicenter study that includes enough patients with sufficient follow-up to definitively determine which patients, if any, should be treated with cytotoxic drugs and which drugs should be used and for how long. Unfortunately, such a study is not even on the horizon. In any event, I now return to the stated goal of the editorial, which is to discuss cytotoxic therapy of idiopathic membranous nephropathy in light of the new insights provided by Imperiale et al. (1), other published reports, and our own experience. Blending these sources of information, I offer the following suggestions.

1) Before embarking on cytotoxic therapy, the patients must be thoroughly evaluated to exclude those with certain secondary causes of membranous nephropathy. Some patients with secondary causes of membranous nephropathy could be worsened by cytotoxic therapy. Such patients include those whose membranous nephropathy is the result of cancer (3), hepatitis B (4), hepatitis C (5), and human immunodeficiency virus (HIV) (6). The nephropathy in the cancer patients is sometimes benefitted by the removal of the cancer (3). The nephropathy in those with hepatitis B or hepatitis C infection might be benefitted by α-interferon therapy (7,8).

Cytotoxic therapy is unnecessary in membranous nephropathy secondary to drugs because stopping the drugs will eventually result in resolution of the nephropathy. Drugs reported to cause membranous nephropathy include nonsteroidal anti-inflammatory agents (9), gold salts, -aptopiril, and penicillamine (10). Chronic exposure to formaldehyde might also be a cause of membranous nephropathy that is benefitted by the removal of the offending agent (11).

Systemic lupus erythematosus (SLE) is an important secondary cause of membranous nephropathy. The SLE can be easily missed because these patients often have none of the usual systemic nonrenal manifestations of SLE and have normal C3 and C4 levels. Our experience indicates that these patients are benefitted by cytotoxic therapy. Nevertheless, it is important to recognize whether SLE is the cause of the membranous nephropathy because of the implications for long-term therapy. The SLE patients with membranous nephropathy can be expected to have many subsequent relapses (renal and nonrenal) and, therefore, require chronic therapy. By contrast, the patients with idiopathic membranous nephropathy usually do not relapse after remission occurs.

2) Do not use cytotoxic therapy in patients with idiopathic membranous nephropathy when favorable prognostic signs are present. The rate of spontaneous remission of nephrotic syndrome in patients with idiopathic membranous nephropathy is 20 to 40%. The patients with complete remission (normal 24-h proteinuria) do not progress to renal failure from membranous nephropathy. By contrast, those with persistent abnormal proteinuria are at increased risk to progression to renal failure (12). Signs indicating a favorable prognosis and, therefore, avoidance of cytotoxic therapy include young age, female gender, nor-
motension, normal serum creatinine level, and mild to moderate proteinuria (e.g., <5.0 g/day) (10,12). In patients with a favorable “profile” (as defined above), adjunctive therapy is recommended. This includes: (a) Control of blood pressure. The Modification of Diet in Renal Disease (MDRD) Study has shown that, in patients with renal disease causing proteinuria ≥1 g/24 h, a decline in GFR is significantly correlated with control of systolic blood pressure. Patients whose systolic blood pressure is controlled in the range of 135 mm Hg lose GFR significantly more rapidly than do those whose systolic blood pressure is controlled in the range of 125 mm Hg (13). Furthermore, the heavier the proteinuria, the stronger is the effect of the higher systolic blood pressure to cause a rapid decline in GFR (13). Thus, “hypercontrol” of blood pressure (sitting systolic blood pressure of about 125 mm Hg) is recommended in patients with idiopathic membranous nephropathy and proteinuria ≥1.0 g/24 h.

(b) Use of angiotensin-converting enzyme (ACE) inhibitor. ACE inhibitors are more antiproteinuric than other antihypertensive agents (14). Proteinuria is a risk factor for the progression of renal disease, but it also appears to be a mechanism of progression of renal disease (15,16). Thus, measures that reduce proteinuria (controlling blood pressure [13], ACE inhibitor therapy [14], and a low-protein diet—see below) appear to be important in the long-term management of the proteinuric patient. Also, ACE inhibitors may have specific renoprotective effects (17) that may require a year or more to be fully expressed (15).

(c) Control dietary protein intake. The MDRD Study has shown that, in patients with proteinuria >1 g/day, reducing the dietary protein intake to about 0.75 g/kg of ideal body weight/day significantly slows GFR loss (terminal GFR slope) compared with a dietary protein intake of approximately 1.1 g/kg of ideal body weight/day (13). In patients with heavy proteinuria (>5 g/day), increasing dietary protein intake by about 1 g/day for each 1 g/day of proteinuria is appropriate to help avoid protein malnutrition.

(d) Control of blood cholesterol level. Animal studies clearly show the benefit of controlling blood cholesterol levels in slowing the progression of experimental renal diseases. The data are less clear in humans (18). Nevertheless, a lipid-lowering diet and, if needed, lipid-lowering drugs are recommended. In patients with severe nephrotic syndrome, the hyperlipidemia is usually refractory to these measures.

(e) Low-dose aspirin therapy. We usually use aspirin, 80 mg daily, as an antithrombotic measure. However, our experience indicates that some thrombotic events will still occur, particularly in those with severe nephrotic syndrome.

(f) Consider the use of steroid therapy. The use of high-dose alternate-day prednisone therapy can be considered in patients with idiopathic membranous nephropathy. However, its use is controversial, particularly because the well-done study by Cattran et al. (19) indicated no benefit of steroid therapy in idiopathic membranous nephropathy, refuting the results of previous studies (reviewed in Ref. 19). However, the Coggins protocol of alternate-day steroid therapy (20) is safe in nondiabetic subjects. We still use this therapy in patients in whom adjunctive therapy (described above) is not achieving its goal (at least a one-third reduction in proteinuria within a few weeks of starting adjunctive therapy), but we are not yet willing to commit to cytotoxic therapy.

(3) Use cytotoxic therapy in idiopathic membranous nephropathy when unfavorable prognostic signs are present. The patients with idiopathic membranous nephropathy who are most likely to have progressive loss of kidney function are those with persistent, heavy proteinuria (e.g., >8 g/day for >6 months), elevated serum creatinine, hypertension, male gender, and over age 50 (10,21). To that list of risk factors, we would add renal biopsy evidence of glomerular sclerosis, and/or interstitial fibrosis superimposed on the membranous nephropathy.

For cytotoxic therapy, we usually use chlorambucil, as in the protocol of Ponticelli et al. (22), but usually do not initiate therapy with the bolus iv steroids as described in that protocol. Instead, we use 15 to 20 mg of prednisone daily throughout the 6-month course of treatment. We have found that serious leukopenia can be avoided in some patients by the use of daily prednisone.

In some patients, we use cyclophosphamide rather than chlorambucil. The starting dose for cyclophosphamide is approximately 1.5 mg/kg of ideal body weight/day, usually for 3 consecutive months (23). Cyclophosphamide can cause bladder toxicity and is more likely to cause serious scalp hair loss than chlorambucil. Both chlorambucil and cyclophosphamide suppress gonadal function and are expensive. However, cyclophosphamide may be the more potent immunosuppressor (23). For this reason, we prefer to use cyclophosphamide in those with elevated serum creatinine levels.

We do not use cytotoxic agents in patients with idiopathic membranous nephropathy whose serum creatinine levels chronically exceed 3.0 mg/dL. Our experience suggests that, at this level of kidney function, cytotoxic therapy has an unfavorable risk/benefit ratio.

If patients relapse after an initial course of cytotoxic therapy, we will generally re-treat them with a full or abbreviated protocol, depending on their response to therapy and associated toxicity (generally, we do not give more than 6 months of therapy with chlorambucil or cyclophosphamide).

If protection of gonadal function is important to the patient, we use leuprolide (Lupron) therapy to induce gonadal arrest (24). This may decrease gonadal injury due to chlorambucil or cyclophosphamide.

During cytotoxic therapy, the white blood cell (WBC) count is measured every 1 to 2 weeks. If the WBC count falls below 5,000/mm³ the cytotoxic drug is stopped until the WBC count is above 5,000/mm³.
The cytotoxic drug is then resumed but at one-half to two-thirds of its previous dose.

We prefer cyclophosphamide over IV cyclophosphamide (23) because of the evidence that po therapy may be more effective at immunosuppression (25), and in our experience, is no more toxic than IV cyclophosphamide. We have rarely observed bladder toxicity from po cyclophosphamide if the dose is approximately 1.5 mg/kg ideal body weight/day (rather than the 2.0 to 2.5 mg/kg, which is often recommended [26] and if the medication is taken all in the morning with extra glasses of fluid at each meal and at bedtime. Also, po cyclophosphamide is very well absorbed from the gastrointestinal tract, is less expensive than IV cyclophosphamide, and has the advantage of providing a cytotoxic effect each day, rather than once every few weeks, as with the usual protocols involving IV cyclophosphamide. Each day, about 2 to 4% of the B cell pool is turned over (27). Thus, a daily immunosuppressive may be more effective than one that is administered at 3- to 4-wk intervals. Generally, we reserve IV cyclophosphamide for those who cannot tolerate po cyclophosphamide. Uncontrolled studies suggest that long-term azathioprine (28) or short-term cyclosporin A therapy (29) may also be effective in idiopathic membranous nephropathy.

In summary, there is ample reason to have faith in cytotoxic therapy in selected patients with idiopathic membranous nephropathy. Nevertheless, it would be heavenly if, in the near future, believers and nonbelievers in cytotoxic therapy could work together to decisively determine its role in the management of idiopathic membranous nephropathy. NIH, will you answer our prayers?

Lee A. Hebert
Columbus, Ohio

REFERENCES