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Idiopathic Membranous Nephropathy
Management Strategies

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Abstract

Treatment of idiopathic membranous nephropathy is based on a 'symptomatic' therapy that includes ACE inhibitors or angiotensin II receptor antagonists, and on an 'aetiological' therapy aimed at modulating underlying immunological mechanisms. The role of the latter is still debated given the usually indolent course of disease; furthermore, traditional immunosuppressants would not have an impact on patient and renal survival according to a systematic review of literature. However, up to 40% of untreated patients eventually develop end-stage renal disease and remission of nephrotic syndrome protects patients from related life-threatening complications and is the strongest positive prognostic factor for long-term kidney function. Therefore, immunosuppressive therapy seems to be rational in high-risk patients with nephrotic syndrome or deteriorating renal function. This article

outlines a possible role for each 'aetiological' therapy on the basis of available evidence in order to provide some practical recommendations. The first-line therapy is based on a 6-month regimen of alternating corticosteroids and an alkylating agent ('Ponticelli' regimen), whereas oral ciclosporin and intramuscular corticotrophin (adrenocorticotrophic hormone) are alternatives that provide comparable results in terms of remission of proteinuria, with a different adverse effect profile. New drugs are emerging as potential treatments, such as mycophenolate mofetil, tacrolimus, intravenous immunoglobulins and rituximab. Specific settings, such as chronic renal failure or elderly age, require a careful balance between benefits and toxicity of immunosuppression. The tailor-made use of this repertoire of drugs can provide a tool to achieve remission of proteinuria and modify the natural course of idiopathic membranous nephropathy.

Membranous nephropathy is the most frequent cause of nephrotic syndrome in adults and accounts for 25% of primary glomerulonephritis according to the Registries of Renal Biopsies.[1,2] While membranous nephropathy can be secondary to tumours, drugs, infectious or autoimmune disease, in two-thirds of patients no causal agent can be identified.[3,4] Treatment of this idiopathic form of membranous nephropathy is the focus of this review.

The natural course of idiopathic membranous nephropathy is variable and not easy to predict. In 20% of patients, a spontaneous complete remission occurs (proteinuria <0.2 g/24 h), whereas up to 40% of patients eventually develop end-stage renal disease (ESRD).[3-5] Complete remission of nephrotic syndrome is the strongest positive prognostic factor in the long-term, whereas entity and persistence of proteinuria and chronic renal failure (CRF) at diagnosis are the main negative factors.[6,7] Severity of renal histological lesions, especially of interstitial fibrosis, is also considered a negative prognostic indicator by some authors.[3,5]

As patients with non-nephrotic proteinuria do not seem to progress to renal failure and are not exposed to nephrotic syndrome-related cardiovascular risk, the general aim of treatment is that of reducing proteinuria to the greatest possible extent.[8,9] This can be achieved either with a symptomatic therapy based on the use of ACE inhibitors and/or angiotensin II receptor antagonists (angiotensin II receptor blockers; ARBs), which could represent the only treatment for low-risk patients with moderate proteinuria, or with an associated aetiologically based therapy with corticosteroids and/or other immunosuppressive drugs in high-risk patients with nephrotic syndrome or deteriorating renal function[10-12] (table I).

Although this approach appears to be reasonable in clinical practice and is recommended by different Italian Guidelines,[7-9,11-13] treatment of membranous nephropathy is the subject of ongoing interest as documented by the number of scientific papers published in the last 20 years (figure 1) and remains controversial, mainly because of the lack of a clear benefit of immunosuppressive regimens on a patient's long-term and renal survival.[14,15]

1. Symptomatic Therapy

Symptomatic therapy includes both drugs aimed at counteracting the effects of nephrotic syndrome and antiproteinuric drugs. All patients with nephrotic syndrome should be given this baseline therapy regardless of whether or not they will also receive a specific therapy in addition.

1.1 Drugs for Nephrotic Syndrome

Drugs for nephrotic syndrome include all categories of diuretics (hydrochlorothiazide for mild forms, loop diuretics for nephrotic syndrome or in the case of advanced CRF, metolazone and aldosterone antagonists), which can be used in

Table I. Idiopathic membranous nephropathy: management strategies[10-12]

Symptomatic therapy
Drugs for nephrotic syndrome
diuretics
HMG-CoA reductase inhibitors
anticoagulants
Antiproteinuric
ACE inhibitors
angiotensin II receptor antagonists (blockers)
Specific therapy
Traditional therapies
corticosteroids
azathioprine
cyclophosphamide
chlorambucil
ciclosporin
corticotropin
New therapies
mycophenolate mofetil
tacrolimus
intravenous immunoglobulins
rituximab

combination to achieve synergy in resistant oedema. Sodium restriction (4–5 g/day of salt) and a moderately low-protein diet (0.8 g/kg/day) appear to be advisable,[16] although the latter remains an area of controversy. While there is evidence that a low-protein diet could have a role in the treatment of nephrotic syndrome, improving albumin and fibrinogen metabolism[17] and helping to achieve nitrogen equilibrium,[18] some studies have not found any advantage in the specific setting of nephrotic syndrome secondary to membranous nephropathy.[19,20]

HMG-CoA reductase inhibitors (statins) are usually necessary to control hypercholesterolaemia, but the rationale for their use also includes their immunomodulatory, anti-inflammatory and antithrombotic properties, which conceivably reduce nephrotic syndrome-related cardiovascular risk.[3]

Prophylactic anticoagulation appears to be advisable at least for patients with massive oedema and an important thrombophilic profile;[3,4,8,21] use of oral anticoagulants may be indicated in patients with serum albumin below 20 g/L, as suggested by Markov-based decision analysis.[22]

1.2 Anti-Proteinuric Drugs

ACE inhibitors and ARBs can be used both to treat hypertension (which is often present) and to reduce proteinuria. They not only have haemodynamic actions (reduction of proteinuria through reduction of intraglomerular pressure) but also directly restore glomerular barrier size selectivity.[23] According to some studies, this would explain their renoprotective effect and would make the use of more toxic immunosuppressive drugs questionable in treating membranous nephropathy, which often has an indolent course and may enter spontaneous remission.[23,24] However, their long-term effectiveness as an alternative to immunosuppressants is still debated.[3,25,26]

2. Specific Therapy

Supporters of a specific immunomodulatory therapy in membranous nephropathy argue that the probability of persistent spontaneous remission does not exceed 30% and that it usually occurs after a considerable period of disease, which lasts on average between 18 and 23 months.[3,5,27] During which time patients are exposed to potentially life-threatening complications of nephrotic syndrome (especially cardiovascular complications)

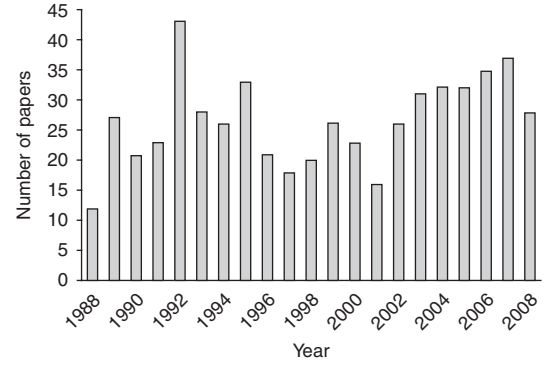

Fig. 1. Histogram showing the number of papers indexed on PubMed concerning treatment of membranous glomerulonephritis in the last 20 years.

and kidney damage can develop as a result of proteinuria, eventually leading to significant renal function deterioration and even ESRD.

However, meta-analyses have not succeeded in gathering conclusive evidence about the long-term superiority of immunomodulatory therapy over a symptomatic therapy with ACE inhibitors or ARBs in terms of 'hard endpoints' such as kidney and patient survival.[15] This may be due to the short follow-up period of the included studies and other limits inherent to meta-analyses and, in our view, does not allow one to overlook the fact that remission of nephrotic syndrome is the only long-term positive prognostic factor for renal function[6,7,28,29] and that it certainly reduces cardiovascular complications of nephrotic syndrome.[13] Therefore, even though reduction of proteinuria and remission of nephrotic syndrome are 'surrogate endpoints', they represent a rational goal.

This article reviews the available evidence on therapies that have been effective in this respect. The first part focuses on more consolidated regimens of therapy, supported by randomized controlled trials (RCTs) and guideline recommendations,[13] while the second part reviews promising new approaches for which evidence is still accumulating and only a few RCTs are available. Finally, adaptations of therapy required by the presence of CRF and elderly age are focused on.

2.1 Traditional Therapies

This review is based on Italian guidelines that have selected 18 RCTs including a total of 1036 patients followed-up for a period ranging from 12 to 120 months (mean = 35 ± 20 months). Fourteen of these studies considered patients with idiopathic membranous nephropathy and normal renal function,[27,30-36] whereas four studies included patients with idiopathic membranous nephropathy and CRF.[37-40]

2.1.1 Corticosteroids

In three RCTs, corticosteroids were not shown to be superior to symptomatic therapy in inducing remission of nephrotic syndrome or preventing ESRD or death.[32-34] However, they were employed in regimens that were probably inadequate (prednisone 125 mg on alternate days for 8 weeks; prednisone 45 mg/m^2 on alternate days for 6 months). It is worth noting that in an Italian study comparing a combination therapy of corticosteroids and chlorambucil versus corticosteroids alone (three pulses of methylprednisolone 1 g followed by oral prednisone 0.5 mg/kg/day for 6 months), remission of nephrotic syndrome in up to 55% of patients was achieved in this latter arm.[3,35]

2.1.2 Azathioprine

In a small RCT, treatment with azathioprine for 1 year, although well tolerated, did not modify either proteinuria or creatinine values when compared with placebo.[31]

2.1.3 Cyclophosphamide

Two RCTs have compared cyclophosphamide, employed alone for 1 year in the first trial and in association with dipyridamole and warfarin for 6 months in the second trial, with symptomatic therapy.[30,36] Treatment with cyclophosphamide tended to achieve remission of nephrotic syndrome in a higher proportion of patients, although the difference did not reach the threshold of statistical significance in the latter study (13/22 vs 6/22; p = 0.067).

2.1.4 Cyclophosphamide or Chlorambucil in Combination with Corticosteroids

Three RCTs by Ponticelli et al.[27,35,41] have studied the combination of cytotoxic agents (either chlorambucil or cyclophosphamide) and corticosteroids in membranous nephropathy. In the first trial, Ponticelli et al.[27] demonstrated that treatment with alternating corticosteroids and chlorambucil protected renal function and increased the chance of remission of nephrotic syndrome in patients with membranous nephropathy. The patients were randomized to receive either alternating 1-month courses of corticosteroids and chlorambucil for a total of 6 months (table II) or symptomatic therapy. After a 10-year follow-up, the percentage of patients who were alive with normal kidney function was significantly higher in the first group than in the second group (92% vs 60%; p = 0.0038) and

Table II. 'Ponticelli' regimen for idiopathic membranous nephropathy. Indications for clinical use in different patient settings[3,13]

Patients	Therapeutic regimen
Patients with normal renal function	Months 1, 3, 5: IV methylprednisolone (1 g for 3 consecutive days), followed by oral prednisone (0.5 mg/kg/day for 27 days) Months 2, 4, 6: chlorambucil (0.2 mg/kg/day for 30 days) or cyclophosphamide (2.5 mg/kg/day for 30 days)
Patients with impaired renal function (GFR <60 mL/min/1.73 m^2) or elderly patients (aged >65 y)	Months 1, 3, 5: IV methylprednisolone (0.5 g for 3 consecutive days), followed by oral prednisone (0.5 mg/kg/day for 27 days) Months 2, 4, 6: chlorambucil (0.12 mg/kg/day for 30 days) or cyclophosphamide (1 mg/kg/day for 30 days)

GFR = glomerular filtration rate; **IV** = intravenous.

61% of treated patients were without nephrotic syndrome (40% in complete remission) versus 33% of untreated controls (5% in complete remission).

In another RCT,[35] the same combination protocol of chlorambucil and corticosteroids was compared with a regimen of corticosteroids alone (3 intravenous pulses of methylprednisolone at months 1, 3 and 5 plus oral prednisone 0.5 mg/kg on alternate days for 6 months) in 92 patients with nephrotic syndrome caused by idiopathic membranous nephropathy. At 1, 2 and 3 years, the percentage of patients who did not have nephrotic syndrome was significantly higher in the first group than in the second (58%, 54% and 66%, respectively, compared with 26%, 32% and 40%; $p = 0.002$, 0.029 and 0.011, respectively). However, at 4 years the difference was no longer statistically significant (62% of the patients in the first group vs 42% of those in the second group; $p = 0.102$) because of the lower number of patients at risk. Of note, in patients treated with the combination of chlorambucil and corticosteroids, the duration of remission was longer than for those of the second group ($p = 0.008$).[30]

Finally, in a third RCT,[41] the same combination of chlorambucil and corticosteroids was compared with one including cyclophosphamide (2.5 mg/kg/day) instead of chlorambucil. While no differences emerged for probability of remission of nephrotic syndrome (82% vs 93%; $p = 0.116$) and in preservation of renal function, severe adverse effects had a tendency to occur more frequently in the chlorambucil group (12% vs 4%).[41]

The strength of these three landmark RCTs lies in the fact that they have provided an effective and well defined regimen in a large homogenous Italian population and were followed-up for a long time. Of the total 174 treated patients, 83% reached remission of nephrotic syndrome and 75% were without nephrotic syndrome after 10 years.[27]

As for the tolerability profile, approximately 9% of patients had to discontinue treatment because of adverse effects. Oncogenic risk has been associated with a cumulative dose of 7 g for chlorambucil and 80 g for cyclophosphamide, which far exceeds those required for the 6-month combination protocol, and the incidence of malignancy was not actually different from that of the general Caucasian population.[41] However, a 3-month treatment with chlorambucil 0.2 mg/kg/day or cyclophosphamide 2 mg/kg/day is sufficient to cause azoospermia; therefore, preservation of seminal fluid before starting therapy is indicated in young patients.[3,41]

Effectiveness of the cytotoxic agent (cyclophosphamide or chlorambucil) in inducing remission of nephrotic syndrome and the superiority of these agents over corticosteroids alone[35] also emerged from two meta-analyses and a systematic review.

In a meta-analysis by Imperiale et al.[42] (based on five RCTs on 228 patients treated with cytotoxic agents and corticosteroids, corticosteroids alone or symptomatic therapy), only treatment with chlorambucil or cyclophosphamide significantly increased the chance of nephrotic syndrome remission (relative risk [RR] = 4.6; 95% CI 3.2, 8.4). Remarkably similar results were provided in another meta-analysis by Hogan et al.[43] (based on seven RCTs on 493 patients; RR for remission of nephrotic syndrome by cytotoxic agents = 4.8; 95% CI 1.44, 15.96; $p < 0.05$).

The Cochrane systematic review (based on 18 RCTs on 1025 patients) has compared four categories of immunosuppressive drugs (corticosteroids alone; cytotoxic agents, either alone or combined with corticosteroids; ciclosporin, either alone or with corticosteroids) and has concluded that only cytotoxic agents allow an increase in complete remission of nephrotic syndrome as compared with symptomatic therapy (RR = 2.37; 95% CI 1.32, 4.25; p = 0.004) and with corticosteroids (RR = 1.89; 95% CI 1.34, 2.67; p = 0.0003). Effectiveness of chlorambucil and cyclophosphamide was similar, but chlorambucil was associated with a higher rate of discontinuation due to adverse effects (RR = 2.34; 95% CI 1.25, 4.39; p = 0.008), especially leukopenia. However, the systematic review highlighted that no classes of drugs had an impact on the combined endpoint of ESRD or death.[15]

Summary Recommendation

A 6-month combination therapy with corticosteroids and cytotoxic agents according to the 'Ponticelli schedule' (table II) yields a high remission rate of nephrotic syndrome (70–80%) and appears to maintain a long-term protective effect at least on proteinuria, at the price of acceptable toxicity. Even if conclusive evidence of an improvement on renal survival is lacking, this is still considered the first-line treatment in patients with nephrotic syndrome secondary to membranous nephropathy. This regimen should not be employed in patients with non-nephrotic proteinuria because they very rarely develop CRF and are not exposed to nephrotic syndrome-induced cardiovascular risks. ACE inhibitors and/or ARBs are usually sufficient to control proteinuria in this low-risk population.

2.1.5 Ciclosporin

Ciclosporin has been used in several uncontrolled studies for its anti-proteinuric properties. Nephrotic syndrome remission rate is around 50–70%. Response usually occurs after 3–7 months of therapy, it may be favoured by small doses of corticosteroids and it is maintained in 40% of patients after ciclosporin discontinuation.[3,13,44] In the only available RCT by Cattran et al.,[45] 51 membranous nephropathy patients with steroid-resistant nephrotic proteinuria were assigned to receive either a 6-month treatment with ciclosporin in combination with low-dose prednisone, or placebo plus prednisone. After an average follow-up of over 19 months, 75% of the ciclosporin-treated group achieved remission compared with 22% of the control group (p < 0.001). Despite a high relapse rate (around 40% by the thirteenth month after withdrawal of ciclosporin), the percentage of patients in remission remained significantly different between the groups until 1-year post-treatment (ciclosporin = 39%, placebo = 13%; p = 0.007) and renal function was stable in the ciclosporin-treated group. Other studies[46,47] employed ciclosporin for a longer period (12 months) with a low-dose corticosteroid (prednisone 0.5 mg/kg/day). This appears to reduce the rate of relapse after ciclosporin withdrawal compared with monotherapy (47% vs 15%). Ciclosporin levels >100 ng/mL and very slow ciclosporin tapering (0.5 mg/kg/month) would also protect against relapses.[46]

However, the main concern with prolonged ciclosporin treatment is nephrotoxicity, which has been well documented in control renal biopsies.[47] An alarming observation is that an increase in immune deposits and a thickening of glomerular basement membrane were detected even in patients with a satisfactory reduction of proteinuria, suggesting continued antibody formation even during therapy.[48] This immunological damage could add to the nephrotoxic insult, making the long-term impact of ciclosporin on renal function in membranous nephropathy difficult to assess.[49,50] However, the relationship between immunosuppression and anti-proteinuric effect of ciclosporin has been recently challenged and a novel mode of action has been proposed; namely, that ciclosporin may directly stabilize actin cytoskeleton of podocytes by increasing resistance of synaptopodin to degradation.[51,52] This action appears to be independent of the effects of ciclosporin on cells of the immune system and could explain why even low-dose therapy with ciclosporin maintains an anti-proteinuric effect.[53]

Summary Recommendation

Italian Guidelines recommend ciclosporin as second-line therapy. Treatment should be continued for at least 1 year at the dosage of 4 mg/kg/day and it should not probably exceed 2 years. Combined therapy with low-dose corticosteroids and slow tapering (0.5 mg/kg/month) helps to minimize relapses. Some studies[44,46] advise renal biopsy before starting ciclosporin to rule out baseline interstitial fibrosis, which contraindicates its use. Although ciclosporin has been used in patients with membranous nephropathy with CRF, a severe reduction in renal function (creatinine clearance <50 mL/min), especially if accompanied by important arterial hypertension, is also a contraindication.

2.1.6 Corticotropin

Promising results have been achieved with corticotropin, which can improve the lipid profile and reduce proteinuria in patients with nephrotic syndrome. The putative mechanism of action of corticotrophin is mediated by its ability to restore glomerular expression of apolipoprotein J (clusterin), which is able to compete with the membrane attack complex C5b-9 for megalin, a receptor located on podocytes, thus preventing complement-mediated lesion of the glomerular capillary wall (figure 2).[54,55] A RCT has compared therapy with corticotropin (1 mg intramuscularly twice weekly for 1 year) with the Ponticelli regimen (table II).[56] Reduction of proteinuria from baseline was significant with both approaches (p 0.049 and p 0.004, respectively) and remission rate of nephrotic syndrome was satisfying and comparable (87.5% for corticotropin vs 75% for the Ponticelli schedule; p = 0.650). However, the authors recommend caution with such therapy in elderly patients and in those who have already been treated with corticosteroids.[56]

Summary Recommendation

As for ciclosporin, evidence of a long-term impact on renal survival are lacking. However, Italian guidelines recommend corticotropin as a second-line therapy for patients with contraindications for combination therapy with cytotoxic agents and corticosteroids or who did not respond to or did not tolerate it.[13] Presence of diabetes mellitus, osteoporosis and previous corticosteroid treatment contraindicate its use.[3,56]

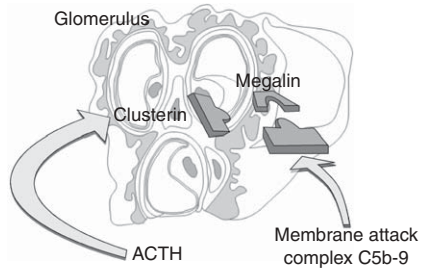

Fig. 2. The putative mechanism of action of corticotropin (adrenocorticotrophic hormone; ACTH) in reducing proteinuria in membranous nephropathy: corticotropin could prevent complement-mediated lesion of the glomerular basement as it restores glomerular expression of apolipoprotein J (clusterin), which is able to compete with the membrane attack complex C5b-9 for megalin, a receptor located on podocytes.

2.2 New Therapies

2.2.1 Mycophenolate Mofetil

Mycophenolate mofetil has been examined in small studies as a treatment for several types of glomerulonephritis including membranous nephropathy at a dose ranging from 500 to 2000 mg for 3–8 months with significant reduction of proteinuria after several months of therapy.[57,58]

In a pilot study,[59] mycophenolate mofetil 2 g/day was administered for 6 months along with prednisolone 0.5 mg/kg/day for 2–3 months to 21 patients with membranous nephropathy, and this regimen was compared with the Ponticelli regimen. There was no significant difference in the rate of remission in two groups (64% vs 80%).

A prospective, open-label RCT also confirmed comparable effectiveness of combined therapy with mycophenolate mofetil and corticosteroids compared with the Ponticelli regimen in 20 patients with membranous nephropathy and nephrotic syndrome followed-up for 15 months. Overall remission rates were similar (63.6% vs 66.7%; p = 1.000), but a lower cumulative prednisolone dose was given in the mycophenolate mofetil group (3.80 ± 0.28 vs 9.93 ± 0.25 g; p < 0.001) and leukopenia was less frequent, suggesting reduced myelotoxicity compared with chlorambucil.[60]

In contrast, in a 1-year RCT in 36 patients, mycophenolate mofetil monotherapy (2 g/day) was not superior to a conservative approach (including renin-angiotensin blockers, statins, low-salt and low-protein diet, and diuretics) in terms of the urine protein to creatinine ratio or remission of nephrotic syndrome. Of note, serious adverse effects occurred in 20% of patients receiving mycophenolate mofetil.[61]

The combination of mycophenolate mofetil and ciclosporin has also been tested in membranous nephropathy.[62]

Summary Recommendations

Mycophenolate mofetil could be a promising alternative to conventional therapy because it allows corticosteroid (or ciclosporin) sparing and is apparently less myelotoxic compared with other cytotoxic agents such as chlorambucil. However, adverse effects (especially gastrointestinal symptoms) occur in a significant proportion of patients at the dosage of 2 g/day. Both dosage and length of treatment remain to be defined.

2.2.2 Tacrolimus

Tacrolimus has been employed as rescue therapy in patients with resistant or relapsing primary glomerulonephritis, including idiopathic membranous nephropathy. The initial dosage of tacrolimus was 0.05 mg/kg/day and it was combined with low-dose prednisolone. After a treatment period of around 29 months, complete or partial remission was achieved in more than 50% of patients, without any significant change in renal function and any relapse in patients with membranous nephropathy.[63,64]

In a RCT by Praga et al.,[65] 25 patients who had received tacrolimus as monotherapy (0.05 mg/kg/day) over 12 months (with a 6-month taper) were compared with 23 untreated controls. While remission in the treatment group occurred in 58%, 82% and 94% of patients after 6, 12 and 18 months, respectively, this was significantly less frequent (10%, 24% and 35%, respectively) in the control group. Six patients in the control group and only one in the treatment group showed deterioration of renal function (defined as a 50% increase in serum creatinine), suggesting that the natural history of membranous nephropathy could have a greater impact on renal function than calcineurin inhibitor nephrotoxicity. The effectiveness of tacrolimus was limited by a high rate of relapse (almost 50%) of nephrotic syndrome, which occurred within 18 months of tacrolimus withdrawal.

In a prospective study in 35 Chinese patients with membranous nephropathy and severe proteinuria (>6 g/day), 24-weeks' therapy with oral tacrolimus (target trough level: 4–8 ng/mL) plus prednisone was compared with intravenous cyclophosphamide (750 mg/m^2 body surface every 2 weeks for the first 8 weeks, then once every 4 weeks for 16 weeks). Complete remission was significantly more frequent in the tacrolimus group (66.7%) than in the cyclophosphamide group (30.8%), and overall percentages of remission (either partial or complete) by 4 and 8 weeks were significantly higher in the tacrolimus group ($p < 0.05$).[66]

Of interest, a pilot study employed a 'sequential' therapy of tacrolimus and mycophenolate mofetil in which the latter was added after a 3-month treatment with tacrolimus and corticosteroids only in patients who still had a proteinuria >1 g/day. In this group, triple therapy was continued for 1 year and a 100% overall remission rate was achieved (complete in 53.3% of patients; partial in 46.7%); however, after an average of 23 months of discontinuation, a high relapse rate occurred (73%).[67]

Summary Recommendations

Tacrolimus could be an effective alternative to conventional therapy. While nephrotoxicity does not appear to be a major problem if low drug trough levels are maintained (4–8 ng/mL), the remarkable effectiveness of tacrolimus is limited by a high rate of relapse after discontinuation, as already observed for ciclosporin therapy.

2.2.3 Intravenous Immunoglobulins

Intravenous immunoglobulins (IVIg) have been employed in several types of glomerulonephritis (especially lupus nephritis) after they proved resistant to conventional therapy, but

there is no RCT supporting their use in membranous nephropathy. However, remission of nephrotic syndrome has been achieved in some patients with a regimen based on serial pulse doses of IVIg (three pulses of 0.4 g/kg for 3 consecutive days, repeated three times at 21-day intervals and followed-up by one pulse every 3 weeks for a 10-month period).[68,69]

In a retrospective study,[70] 30 patients followed-up for at least 5 years received 1–3 courses of IVIg at the dosage of 5–10 g/day (100–150 mg/kg/day) for 6 consecutive days. Patients were divided into the following two groups on the basis of electron microscopy details of immune deposits on glomerular basement membrane: (i) homogeneous type (reflecting synchronous 'early' deposits); and (ii) heterogeneous type (reflecting coexistence of deposits at different stages of evolution). Interestingly, 6 months after treatment, IVIg therapy had induced earlier remission in patients with the homogeneous type compared with a similar group of patients treated with corticosteroids alone or in combination with cyclophosphamide (57% vs 10%, respectively, $p = 0.006$). This difference was not observed in patients with the heterogeneous type. This may suggest that IVIg therapy is effective only at an early stage of the evolution of membranous nephropathy. However, there was no significant difference in long-term renal survival for all groups.[70] Therapy was well tolerated and there were no reports of acute renal failure, a rare complication due to tubular toxicity as a result of sucrose being employed as a stabilizer of IVIg products.[71] Short treatment protocols have also been employed with success in some patients, whereas longer regimens could be needed in non-responders.[72]

Summary Recommendations

IVIg may increase the likelihood of remission when used at an early stage, but it does not appear to have an impact on the long-term prognosis of membranous nephropathy. Therapy seems to be well tolerated and could be useful in patients with an active infection, which contraindicates use of immunosuppressants. Dosage and length of treatment remain to be defined.

2.2.4 Rituximab

Rituximab, a monoclonal antibody that deletes B cells by binding to the CD20 surface antigen,[73] has been used in small samples of patients.[74,75] In one study of 14 patients with nephrotic syndrome, rituximab 375 mg/m^2 weekly for 4 weeks resulted in a decrease in proteinuria only in patients with mild tubulo-interstitial lesions at renal biopsy, whereas no effect was observed in patients with more advanced histological damage.[76] In another study, 15 patients received rituximab 1 g twice (repeated after a 15-day interval) and a second course at 6 months if nephrotic proteinuria persisted. Response at 12 months was extremely variable from complete remission (in 2 of 15 patients) to no effect.[77] Interestingly, the authors found no relationship between the response and number of B cells in the blood and CD20+ cells in the kidney biopsy, and clinical and histological features at presentation. Therefore, elements that may predict patients who may benefit from this drug are unclear, although presence of severe tubulo-interstitial lesions is associated with a poor response.[78,79] The impact of rituximab therapy on histological lesions has been the focus of a recent analysis by Ruggenenti et al.[79] Repeat renal biopsies of patients who had entered stable nephrotic syndrome remission after four weekly rituximab (375 mg/m^2) infusions demonstrated reabsorption of subepithelial deposits and regression of the glomerular barrier lesions responsible for proteinuria, with an increase in the total number of 'slit diaphragms'. The same authors have also recently achieved permanent remission of nephrotic syndrome in patients with membranous nephropathy by employing a single infusion of rituximab in a subset of patients who showed prolonged depletion of B cells,[80] thus reducing risks of adverse effects and costs.

Summary Recommendations

Rituximab is a promising drug that could directly interfere with production of pathogenetic antibodies in membranous nephropathy. Tolerability appears good. However, response is variable, and dose and length of therapy are still to be defined.

3. Specific Clinical Settings

3.1 Patients with Membranous Nephropathy and Chronic Renal Failure

Treatment of membranous nephropathy in patients with deteriorating renal function has a strong rationale because these patients are at risk of developing ESRD. However, adverse effects of immunosuppressive drugs, especially infections, are more frequent in patients with CRF than in populations with normal renal function and their effectiveness is modest if established chronic histological lesions are already present. Therefore, the following general conditions should be met before immunosuppressive therapy is started in patients with CRF secondary to membranous nephropathy:[81]

- Nephrotic syndrome must be present (recovery of renal function appears to be secondary to remission of nephrotic syndrome, which reflects a glomerular immunological activity still susceptible to treatment).
- Tubulo-interstitial damage must be absent or mild (presence of moderate to severe lesions in this area reflects established long-term damage triggered by persistent proteinuria, which is unlikely to be reversible even if immunosuppressive drugs achieve reduction of proteinuria). Renal biopsy should be performed in this setting if renal dimensions allow it, to gather information, in particular, on the degree of interstitial fibrosis and glomerulosclerosis.[82]
- Renal function must not be severely compromised. A serum creatinine exceeding 3–4 mg/dL generally contraindicates immunosuppressive therapy because benefits become unlikely. However, even in advanced CRF, there is no evidence of a point of no return, and improvement or stabilization of renal function can be achieved in selected patients through a tailor-made, individualized regimen of immunosuppressive therapy.[9,83]
- In the presence of a rapid functional deterioration in membranous nephropathy, an associated type of renal insult or a secondary form of membranous nephropathy (i.e. drug-induced) must be ruled out, i.e. renal vein thrombosis,[84] extracapillary proliferative glomerulonephritis[85-88] and acute interstitial nephritis.[89]

Most studies, although of limited size, are based on two immunosuppressive approaches: a combination therapy with corticosteroid and chlorambucil, which represents the first-choice treatment, or ciclosporin therapy.[83] Mycophenolate mofetil also deserves to be mentioned.

In a RCT, 6-months' oral combination therapy of corticosteroids and chlorambucil was more effective than an intravenous combination of cyclophosphamide and methylprednisolone pulses in improving renal function.[90] As Passerini and Leoni[81] pointed out in a recent review, the overall results of regimens based on monotherapy with corticosteroids or cyclophosphamide pulses are not satisfactory. However, other small studies with limited follow-up[91-93] suggest that a combination regimen with oral corticosteroids and an alkylating agent can result in a partial or complete remission of proteinuria in 65% of patients treated with cyclophosphamide and in 30% of those treated with chlorambucil, with an improvement of renal function in 40% of patients.[9,83] These results include the onset of adverse effects in up to 70–100% of patients, including infections (especially pneumonia and viral infections), bone marrow suppression and cancer. Therefore, doses of methylprednisolone pulses and of cytotoxic agents should be halved in patients with CRF, as outlined in table II.[3] Frequent monitoring of white blood cell count is necessary to avoid leukopenia.

Ciclosporin represents a possible alternative in terms of tolerance profile. In a small RCT, Cattran et al.[39] employed ciclosporin (3.5 mg/kg/day) for 1 year in nine patients with nephrotic syndrome and CRF (glomerular filtration rate [GFR] approximately 50 mL/min/1.73 m^2) achieving a 60% reduction in proteinuria and a progressive recovery of renal function (improvement in creatinine clearance slope by 1.7 mL/min per month, which lasted for 2 years after the end of therapy. However, cumulative results failed to show a protective effect of ciclosporin on incidence of ESRD compared with symptomatic therapy. These data suggest caution in the use of calcineurin inhibitors in the setting of worsening

renal function because nephrotoxicity and increase in arterial hypertension could outweigh the benefits in the long term.[50]

Finally, mycophenolate mofetil represents an alternative to ciclosporin in CRF because of the lack of nephrotoxicity. Branten et al.[94] employed mycophenolate mofetil (at a dosage of 2 g/day) in association with a 6-month corticosteroid course (three 1 g methylprednisolone pulses at alternate months followed by oral prednisone 0.5 mg/kg/day) and achieved a mean 77% reduction in proteinuria and partial recovery of renal function (increase of 20% in creatinine clearance). However, these results were not superior to those achieved in a historical control group of patients treated with cyclophosphamide, and drug toxicity (especially bone marrow depression) was comparable.

3.2 Elderly Patients

Membranous nephropathy represents the most important cause of nephrotic syndrome in patients aged >65 years[1,2] and poses unique challenges for the following reasons:[95-98]

- Diagnosis of primitive, 'idiopathic' membranous nephropathy is more demanding because it requires a thorough examination to rule out a secondary cause, especially occult solid tumours such as carcinoma of the lung and the gastrointestinal tract, which would obviously contraindicate any immunosuppressive therapy.
- Elderly patients often present with some degree of CRF, due to coexisting vascular disease and/or to the physiological decline in GFR with age.
- Elderly patients often have immune-system alterations that make immunosuppressive drugs more toxic and infectious complications more frequent. Therefore, an aetiological treatment should be considered on an individual basis taking into account the patient's clinical features and co-morbidities, life expectancy and histological prognostic elements.

On this basis, most studies[95,96] suggest that immunosuppressive therapy should be reserved for patients at high risk of progression to ESRD, such as those with advanced CRF (GFR <45 mL/min/1.73 m^2) or an increase in serum creatinine of >25% or a severe persistent nephrotic syndrome not responding to symptomatic treatment. High urinary excretion of β_2 microglobulin and IgG also seem to predict an increased risk of ESRD regardless of renal function impairment.[99]

First-line treatment consists of prednisone and cyclophosphamide at a reduced dosage (the same adjustment suggested for CRF also applies to age of >65 years), whereas ciclosporin could be used as a second option in patients who do not respond to standard therapy, provided that GFR exceeds 50–60 mL/min/1.73 m^2. Response rates do not significantly differ from those observed in other age groups. High-dose corticosteroids should be avoided when possible, especially in the presence of diabetes, severe vasculopathy or osteoporosis, and a rapid tapering is recommended.[96,97]

4. Conclusions and Recommendations

We can outline some practical recommendations on the basis of the available evidence, following guidelines from the Italian Society of Nephrology.[13]

Treatment of idiopathic membranous nephropathy includes a symptomatic approach with antiproteinuric drugs (ACE inhibitors and/or ARBs), which some studies recommend combining with a low-protein and low-sodium diet,[16-18] with the addition of statins, and low-dose aspirin or anticoagulants in the presence of nephrotic syndrome. If patients are at risk of developing CRF or ESRD (persistent and/or severe nephrotic syndrome, deteriorating renal function, severity of lesions at renal biopsy) an aetiological therapy with corticosteroids and/or other immunosuppressive drugs must be added with the aim of inducing remission of nephrotic syndrome.[3,6]

Although a systematic Cochrane revision has not provided any conclusive evidence that 'hard endpoints' (long-term renal or patient survival) are modified by any traditional immunosuppressive drugs,[15] remission of nephrotic syndrome remains a rational goal because it protects the

patient from related life-threatening complications and it has a nephroprotective effect.

In asymptomatic patients without nephrotic syndrome, a 6-month observation period is advisable to monitor proteinuria and response to therapy with ACE inhibitors or ARBs. However, in patients with nephrotic syndrome, aetiological therapy should be started immediately.[13]

A 6-month combination therapy with alternating corticosteroids and chlorambucil or cyclophosphamide (Ponticelli regimen) can be currently considered as the first-line treatment after careful evaluation of oncogenic risk and gonadotoxicity.[3,27] Alternatively, a 1-year treatment with corticotropin intramuscularly can be considered[54-56] provided that the patient has not previously received corticosteroid treatment. Ciclosporin therapy is another alternative, especially for patients with severe nephrotic syndrome that has relapsed after the Ponticelli regimen, and who have a normal renal function and no interstitial lesions at renal biopsy.[44,46] Calcineurin inhibitor nephrotoxicity remains a major concern, but it can be minimized with low doses of ciclosporin. On the other hand, relapses after discontinuation can be reduced by maintaining ciclosporin levels >100 ng/mL and tapering ciclosporin very slowly (0.5 mg/kg/month).[47-50,53]

Several drugs that are used in the field of transplantation and autoimmune disease have been recently applied to membranous nephropathy, but their role is still to be defined.

The use of mycophenolate mofetil,[57-62] tacrolimus,[63-67] IVIg[68-72] and rituximab[73-80] can be considered in selected patients who have not responded to traditional therapies or have relapsed after treatment or have contraindications. Rituximab is especially interesting because it depletes CD20+ B lymphocytes, which are involved in the pathogenesis of membranous nephropathy, although response rate is highly variable.[77]

Treatment of patients with CRF[81-83] or elderly age (>65 years) requires a careful balance between possible benefits and increased toxicity of immunosuppressive drugs.[95-97] First, the presence of undiagnosed tumours should be ruled out in the elderly (secondary membranous nephropathy).[98] The therapeutic decision concerning the use of an aetiological agent should then be individualized and the dosage of immunosuppressant adjusted to minimize adverse effects, especially infections.

A combined approach with symptomatic antiproteinuric drugs and immunosuppressants in high-risk patients with nephrotic syndrome can favour a partial or complete remission in a high percentage of patients. Sequential therapy with drugs that have different mechanisms of action also seems promising. Therefore, in our view, the possibility of a benign evolution of membranous nephropathy with spontaneous remission should not justify therapeutic nihilism,[10-12,14] especially if we bear in mind that membranous nephropathy can eventually lead to ESRD in up to 40% of patients.[5]

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