Outcomes Research in Glomerulonephritis

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Glomerulonephritis remains the second or third most common primary renal disease type to progress to end-stage renal failure. This disease type is particularly important because its focus is limited to the kidney and its reversal or stabilization ensures a return to a normal quality of life for the individual. Also, because its highest incidence rate is in childhood and early adulthood, the implications of effective therapy in terms of preventing end-stage renal failure costs, benefits not only the individual but also society. We focus on the 3 most common variants that progress to end-stage renal failure (ie, membranous nephropathy [MGN], focal segmental glomerulosclerosis [FSGS], and IgA nephropathy). Together these represent approximately 80% of the primary glomerular diseases known to progress. We discuss the outcome studies published over the past decade in these disorders that permit the best insight into specific immunotherapy. We provide this data in an evidence-based model so the reader can appreciate the strengths and/or weaknesses of the therapies discussed and we provide a framework for clinical management.

GLOMERULONEPHRITIS (GN) remains the most common renal limited disease leading to end-stage renal failure. The most frequent histologic types are membranous nephropathy (MGN), focal segmental glomerulosclerosis (FSGS) and IgA nephropathy. All of these disorders have secondary causes but it is the idiopathic variant that falls within the scope of this article. The associated features that occur with most types of progressive renal disease including hypertension, hyperlipidemia, and thromboembolic events are not discussed, although their management is known to slow renal disease progression and/or to reduce comorbid conditions and therefore should be applied to all patients.

We restrict our review to immunomodulatory therapeutic trials in these 3 variants of glomerulonephritis and provide a therapeutic framework derived from this evidence-based medicine. Tables 1 and 2 outline the levels of evidence for rating studies of treatment, prevention, and quality assurance that are used in this article.

We use this approach to treatment trials in each of the different histologic categories after a brief description of their natural history. We incorporate strategies currently available to identify the patients at the highest risk for progression because this is a variable that often limits the generalizability of specific therapies.

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Supported in part by the Canadian Institutes for Health Research - New Emerging Team grant no. 54004, the Genes, Gender, and Glomerulonephritis Group.

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0270-9295/03/2303-0004$30.00/0
doi:10.1016/S0270-9295(03)00062-7

MGN

MGN is the most common cause of adult-onset nephrotic syndrome.[1,2] It remains among the leading cause of end-stage renal disease owing to glomerulonephritis. Despite its frequency, many debate its specific management related to issues such as the identification of the patients most likely to progress, how long to wait before instituting specific treatment, and what immunomodulatory therapy should be used. The majority of cases of MGN are idiopathic in nature, although up to one-third have been associated with a specific etiology.[3] Although MGN has been the most common histologic type associated with the nephrotic syndrome in industrialized countries for the past 50 years, FSGS has been emerging in some studies as the new number one type. Part of this trend may relate to inclusion of large numbers of patients of African-American origin in whom FSGS has a higher incidence than MGN.[4,5] Clinical features at diagnosis or time of biopsy examination are quite variable. Although the majority present with features of the nephrotic syndrome, the development of MGN can be quite insidious and it is often only with the development of clinical signs of edema that the patient seeks attention. Fifty percent of patients have microscopic hematuria at time of biopsy examination and 30% to 50% have hypertension even in the absence of renal insufficiency. Hypertension is particularly common in the older

Table 1. Levels of Evidence of Rating Studies of Treatment, Prevention, and Quality Assurance

1) RCT that showed a statistically significant difference in at least one important outcome (eg, survival or major illness).
OR
2) An RCT that does not meet the level 1 criteria
3) A nonrandomized trial with contemporaneous controls selected by some systematic method (ie, not selected by perceived suitability for one of the treatment options for individual patients)
OR
Subgroup analysis of a randomized trial
4) A before-after study or case series (of at least 10 patients) with historic controls or controls drawn from other studies
5) Case series (≥10 patients) without controls
6) Case reports (<10 patients)

MGN patient but its relationship to disease as opposed to age per se is not clear.[6]

The hallmark finding in membranous nephropathy on pathology is the presence of subepithelial immune deposits best seen on electron microscopy. The specific light, immunofluorescence, and electromicroscopy findings are beyond the scope of this article but are well described in renal pathology textbooks.

NATURAL HISTORY

We cannot rationally discuss treatment of MGN without a clear understanding of the natural history of the disease. Unfortunately, this remains difficult to characterize owing to a limited number of studies of untreated subjects. A review of the quality of studies already published and used to describe the natural history of this condition reveals the multiple inconsistencies that contribute to this difficulty.[7] In general, however, extraction of the best data available from either reviews that have combined studies of treated and untreated patients[8] or large pooled analyses of more than 30 studies[9] have estimated renal survival at 10 years between 65% and 85%. An unexpected and unrecognized factor in the majority of these studies is the high mortality rate from nonrenal causes varying from 6% to 20%. An as yet unidentified element of glomerulonephritis may increase the risk for mortality as suggested by a recent review of over 2,300 cases of glomerulonephritis.[10] In this evaluation of glomerulonephritis 32% of the subjects had died by 10 years. MGN was listed as a low-risk group with a relative mortality only 3 times that of the general population. One of its most unusual qualities compared with other types of glomerulonephritis is a spontaneous remission rate of between 20% and 30%.

PROGNOSTIC FACTORS

Given the overall wide variability in outcome of this disease it is useful to isolate factors that identify individual patients at risk for progression before discussing potentially hazardous immunosuppressive routines. In univariate analysis male gender, advanced age, hypertension, renal insufficiency, and severity of urine protein excretion at presentation all appear to be predictive of a poor outcome. Men have been identified to have a significantly worse prognosis going back to studies in the early 1980s. Several population studies have observed that the gender ratio is almost equal at presentation,[11] whereas at end-stage renal disease it is consistently 2 to 1 or greater for men and women.[12] This suggests a higher spontaneous remission and/or a slower progression rate in women. Our own long-term observational data support this contention. We found by multivariate analysis only 2 factors associated with spontaneous remission, persistent subnephrotic proteinuria and female gender.[13] A recent meta-analysis has confirmed this finding. Older age has long been associated with a higher percentage of patients developing end-stage renal failure. Recent studies have suggested that renal reserve is limited in the elderly patient and hence although the rate of deterioration is not quicker, the renal function start point is lower, thus ensuring a poorer prognosis. Nephrotic range proteinuria, renal insufficiency, and tubular interstitial changes on pathology also have been found to be fairly consistently associated with a poor prognosis

The major problem with all of the earlier-described features is the lack of specificity and their qualitative nature. Another approach has been to use dynamic changes in the clinical parameters

Table 2. Grading System for Recommendations

A The recommendation was based on one or more studies at level 1
B The best level of evidence available was at level 2
C The best level of evidence available was at level 3
D The best level of evidence was lower than level 3 and included expert opinion

Table 3. Results of Model Fitting and Validation

	Toronto	Finland	Italy
Chronic renal insufficiency	47/184 (26%)	13/78 (17%)	25/101 (25%)
Sensitivity	93%	100%	84%
Proteinuria >3.5 g/d	89%	77%	60%
model			
Specificity			
Proteinuria >3.5 g/d	38%	30%	17%
model	86%	89%	92%
Positive predictive value			
Proteinuria >3.5 g/d	34%	24%	25%
model	67%	59%	64%
Negative predictive value			
Proteinuria >3.5 g/d	94%	100%	76%
model	94%	95%	82%
Accuracy			
Proteinuria >3.5 g/d	53%	43%	34%
model	85%	87%	79%

over time to produce a semiquantitative risk for progression.[14] This approach incorporates the clinical parameters of proteinuria and creatinine clearance estimates over fixed periods of time. A validation study further simplified the algorithm by limiting this fixed period to 6 months. As shown in Table 3, the sensitivity of initial nephrotic range proteinuria is high but its specificity and positive predictive values are low, ranging between 17% and 38%. The use of the model improves both these parameters to the range of 60% to 90% and the overall accuracy to between 80% and 90%.

Examples of the application of the model to hypothetical cases are shown.

Logistic regression model:

$$X = 1.26 + 0.3 * PP - 0.3 * \text{slopeCcr} - 0.05 * Ccr_i$$

Where PP is the level of persistent proteinuria in g/24 h. This is measured as the lowest level observed over a period of 6 months. SlopeCcr is the slope of the creatinine clearance over the period used to observe persistent proteinuria (eg, 6 mo), measured in mL/min/month^{-1}. Ccr_i is the initial creatinine clearance documented at the beginning of the observation period, in mL/min.

Use the calculated X to obtain a probability of progression (R) by substituting as follows:

$$R = \frac{e^X}{(1+ e^X)}$$

Sample calculation of risk for progression:

Patient A:

Month	Proteinuria (g/24 h)	Creatinine Clearance (mL/min)
0	10	90
3	6	90
6	4	90

We can now estimate patients A's risk for progression by calculating the following.

$$PP = 4 \text{ g/24 h}$$

SlopeCcr = Ccr final − Ccr initial = 90 mL/min − 90 mL/min = 0

Time 6 months

Initial Ccr = 90 mL/min.

$X = 1.26 + (0.3 * PP) - (0.3 * \text{slope Ccr}) - (0.05 * Ccr_i)$

$= 1.26 + (0.3 * 4) - (0.3 * 0) - (0.05 * 90)$

$X = -2.04$

$eX = 0.13$

R = (0.13 / 1.13) * 100 = 11% risk for progression.

On the other hand, if the proteinuria remained at 10 g, and the initial Ccr was only 80 mL/min but the creatinine clearance did not change over 6 months, the estimated risk for progression would increase to:

$$X = 1.26 + (0.3 * 10) - (0.3 * 0) - (0.05 * 80) = 0.26$$

$$e^X = 1.30$$

$$R = 1.3(1 + 1.3)$$

$$R = 56\% \text{ risk for progression.}$$

It is important to remember that the individual risk factors of age, gender, pathology, hypertension, and renal insufficiency remain but they do not add to the predictive value of this algorithm.

TREATMENT

This article is focused on specific immunotherapy although it is recognized that nonimmunologic approaches, such as dietary protein restriction, antihypertensive treatment, and others, also are important and proven additive therapies in the management of MGN.

SPECIFIC IMMUNOTHERAPY

Given the variable clinical outcomes alluded to in the Natural History section it is important to first establish categories of risk for progression before considering specific immunotherapy. We used our predictive algorithm to create 3 such strata. We then examined the available therapeutic studies and categorized their trial patients by the profile of their subjects' initial laboratory characteristics. This allowed us to separate the effectiveness of any therapy by the category of risk for progression of the patients in the study. By using this strategy, the assignment of an individual patient into their risk category will allow treatment options to be developed based on best evidence. It also will provide a better picture of the risk/benefit ratio for any specific treatment for both the patient and the physician.

RISK FOR PROGRESSION CATEGORIES AND TREATMENT

Low Risk for Progression

The definition of low risk is an asymptomatic patient with normal creatinine clearance at presentation, peak proteinuria less than 4 g/d, and stable renal function over the 6 months of observation.

Prognosis of these patients is excellent. In our validation study[15] approximately 25% of MGN patients fit this category and only 5% showed progression over a mean observation period of 6 years. Blood pressure management and antiproteinuric strategies with agents such as the angiotensin-converting enzyme (ACE) inhibitors should be used in this group but given the general favorable outcome, immunosuppressive therapy is not recommended. Because a small percentage will progress and/or change categories with time, ongoing monitoring of renal function, proteinuria, and blood pressure is recommended.

Medium Risk for Progression

The definition of medium risk is normal creatinine clearance at presentation that remains unchanged during the 6 months of observation but proteinuria remaining between 4 and 8 g/d over that period.

Corticosteroids alone in these medium-risk patients have proven to be ineffective in inducing remission and although some have indicated transient improvement in proteinuria, none of the level one studies published in the past 2 decades have indicated progression is prevented.[16,17] One level one study in the 1970s had suggested preservation of renal function with corticosteroids alone but no improvement in proteinuria, a result difficult to explain given our recent recognition that not only duration of proteinuria but quantity are the major risk factors related to progression.

When corticosteroids are combined with a cytotoxic agent a significant benefit has been described in the treatment of this risk group. A significant increase in both remission of proteinuria and renal survival was shown in a 10-year follow-up of a study comparing a regimen of prednisone and chlorambucil with symptomatic treatment only.[18] This regimen consisted of a 6-month treatment period with the first 3 days of months 1, 3, and 5 to include 1 g of intravenous methylprednisolone followed by 27 days of oral methylprednisone at 0.5 mg/kg/d. In the alternating months (2, 4, and 6) chlorambucil 0.2 mg/kg/d was used instead of the corticosteroid. At 10 years the probability of renal survival was 92% in the treatment group and 62% in those receiving symptomatic therapy ($P = .004$). During the follow-up period the probability of achieving a complete or partial remission was 83% in the treatment group and only 38% in the control group ($P = .000$). A further trial from the same group substituted cyclophosphamide at 2.5 mg/kg/d for the chlorambucil in months 2, 4, and 6 and showed a similar short-term benefit.[19] There was an approximate relapse rate of 30% in both groups by 2 years. The regimen was well tolerated

with only 10% discontinuing treatment owing to adverse effects (level 1).

The effectiveness of cyclosporine in combination with low-dose prednisone in this risk category of patients has been published recently.[20] All of the 51 patients in this study had failed to achieve remission after a minimum of 8 weeks of prednisone at 1 mg/kg/d. In this single blind study, cyclosporine, given at 3.5 mg/kg/d divided into 2 doses with a target whole-blood trough level of 125 to 225 ng/mL, was compared with placebo. All patients were given low-dose prednisone at 0.15 mg/kg/d up to a maximum of 15 mg/d. At the end of treatment at 26 weeks, 75% of those receiving cyclosporine versus only 22% of controls had achieved either a partial or a complete remission ($P = .001$). Relapses were common with approximately 40% of the treatment group relapsing. The fraction of patients remaining in remission at the end of 18 months remained significant, in favor of the cyclosporine-treated group (ie, 39% versus 13% placebo group) ($P = .007$). No significant change in renal function or renal survival was noted in either group over the observation period of 2 years (level 1).

High Risk for Progression

The definition of high risk is persistent proteinuria of 8 g/d or greater over the 6 months of observation with or without initial renal impairment and/or deteriorating renal function during this time frame.

This subgroup of MGM patients is small and represents no more then 10% of the total population. In the one randomized study of corticosteroids alone in high-risk subjects (mean proteinuria at entry of 10.6 g/d), prednisolone at 100 to 150 mg on alternate days for 8 weeks plus a taper did not confer benefit with respect to either proteinuria or renal function during the 3-year observation period (level 1).[21] An earlier small, retrospective, uncontrolled study of 15 patients with declining function suggested 5 days of 1 g/d methylprednisolone followed by a tapering course of prednisolone was associated with initial stabilization in 9 of 15 subjects. However, at last follow-up evaluation, 2 patients had died and 5 patients had reached end-stage renal disease, suggesting the positive benefit of the treatment was transient (level 5). Four studies have examined the use of chlorambucil plus corticosteroids by using a modified version of the Italian regimen in patients at high risk for progression. Substantial improvement in renal function was observed in approximately 50% of these patients associated with a decline in proteinuria.[22] In most cases with initial severe renal insufficiency, however, progressive deterioration in function continued. The outcome of these patients were compared with historic controls and there did appear to be a trend to improve survival (level 5).[23] There was a significant incidence of serious complications in this study related to infectious and myelosuppressive effects necessitating discontinuation of the medication in over one third of the patients. Most recently, a study of 39 subjects treated with a regimen of oral chlorambucil 0.15 mg/g/d for 14 weeks plus oral prednisone tapered over a 6-month period was compared with a historic control group treated conservatively.[24] All patients in both groups had documented severe proteinuria greater than 7 g/d plus an increasing serum creatinine level during the 6 months before entering the study. At entry their creatinine levels were greater than 2 mg/dL. At 4 years of follow-up evaluation, those receiving the chlorambucil/prednisone routine had a 90% probability of renal survival compared with only a 55% probability in those receiving conservative therapy P less than .001 (level 4).

On the other hand, monthly pulse cyclophosphamide for 6 months in addition to oral prednisone has been compared with prednisone alone in 36 patients who qualified as high risk by virtue of renal insufficiency.[25] No benefit was determined after 2 years of follow-up by the addition of the pulse cyclophosphamide (level 2). Earlier studies that involved long-term oral cyclophosphamide had suggested a benefit but there were significant long-term side effects from this routine (level 5). Another group recently has compared intravenous cyclophosphamide replacing the chlorambucil in a small group of patients and showed no benefit after 1 to 3 years of follow-up evaluation (level 5). Most recently, when the Italian regimen was modified (ie, chlorambucil reduced to 0.15 mg/d) and compared with a lower dose of cyclophosphamide (1.5–2 mg/kg/d for 1 y) plus steroids, the cyclophosphamide group showed a greater benefit with a larger decrease in serum creatinine level, lower incidence of end-stage renal disease, more frequent remission of proteinuria, as well as fewer short-term side effects than the chlorambucil routine (level 3).

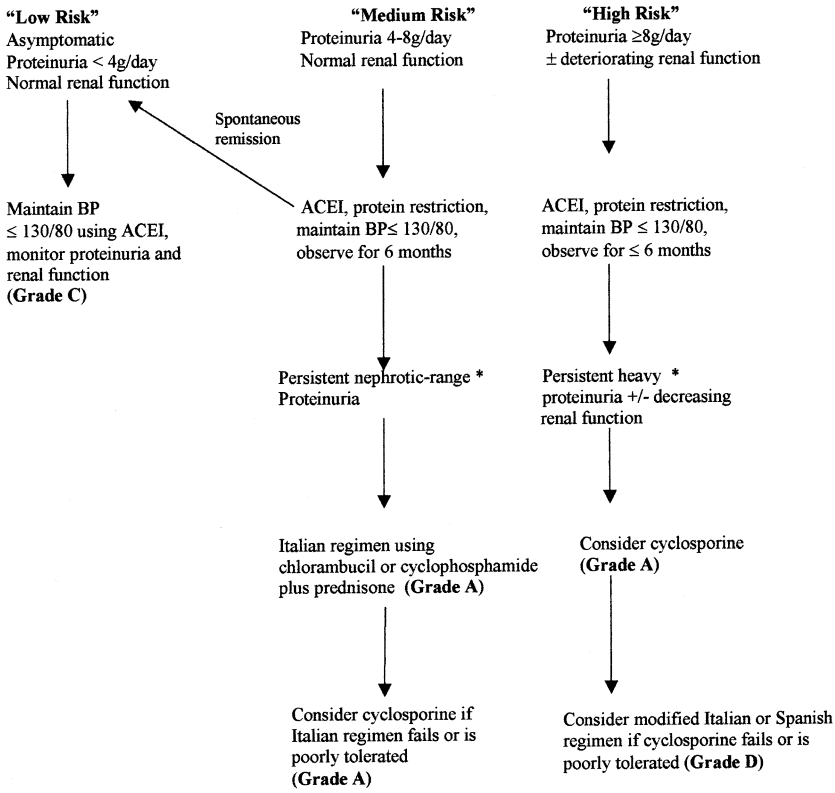

Fig 1. Treatment algorithm for the management of idiopathic MGM. Patients may change from one category to another during the course of follow-up evaluation. BP, blood pressure; ACEI, ACE inhibiting drug. *Introduce appropriate risk-reduction strategies.

Cyclosporine has been examined in this population by more than 1 investigator but there has been only one randomized controlled trial in patients with documented progressive renal insufficiency before trial entry.[26] One year of cyclosporine alone was compared with placebo. Cyclosporine-treated patients showed significantly reduced proteinuria and a slowing in the rate of deterioration of renal function as measured by creatinine clearance and reciprocal of creatinine, ie, 1/cr. The positive results were sustained in more than half the patients as late as 2 years after the treatment had been discontinued (level 1). A recent retrospective review from a large collaborative group treated 41 patients considered at high risk for progression owing to the severity of their proteinuria (mean, >0 g/d) and their resistance to other immunosuppressive therapy.[27] They found that 34% of their patients achieved a complete remission after a mean treatment time of 225 days with a mean dose of cyclosporine of 3.3 mg/kg. This supports the efficacy of cyclosporin but suggests a more prolonged course before assuming resistance (level 5).

A treatment algorithm integrating these studies is given in Figure 1.

NEWER THERAPIES

Mycophenolate mofetil (MMF) is a new immunosuppressive agent that preferentially inhibits purine synthesis in activated lymphocytes. Two uncontrolled studies have used MMF in the treatment of idiopathic MGN. In the first pilot study the 16 patients, who would be categorized as either medium or high risk for progression by virtue or their renal parameters, were treated with 1.5 to 2 g/d of MMF for a mean of 8 months. Some success was noted with 6 of their 16 patients achieving a 50% reduction of their proteinuria.[28] None of their patients had further deterioration of renal function during the observation period. A more recent pilot study with MMF included 17 patients with MGM. Again, modest success was indicated (level 5).[29] Side effects were infrequent and a controlled trial with this agent seems warranted. The most recent agent described in the treatment of MGN is Rituximab, a monoclonal antibody direct against the surface antigen CD20 of B cells. All of their patients ($n = 21$) remained nephrotic despite full doses of ACE inhibitor and some had impaired renal function.[30] The mean urine protein level had

decreased by approximately 50% by 24 weeks, with 2 patients achieving a full remission and 3 patients achieving a partial remission by that time. Adverse effects were reported as mild although 2 patients had an anaphylactic reaction with the infusion (level 5)

FSGS

FSGS is the most common of the primary glomerulonephritis types to lead to end-stage renal disease in children and young adults.[12] Although the percentage of the total within the glomerulonephritis category in FSGS is lower in adults (22%) than children (33%), in absolute numbers in the period from 1993 to 1995 adults outnumbered children 10:1.[12] In most cases the exact cause of this lesion remains unknown. Recently, genetic mutations of components of the epithelial cell slit diaphragm have been suggested to be responsible for up to 20% to 25% of cases in children but their relationship to steroid resistance, response to therapy, and whether additional elements are required for phenotypic expression remain important unexplored areas.[31,32] Certainly, this is a heterogeneous condition that is not universally responsive to immunosuppression or corticosteroids. Hypertension and renal dysfunction are common findings at presentation. In the late 1970s this histologic diagnosis in adults was felt to portend futility in treatment with a reported response rate to corticosteroids of 10% to 12%.[33] This prognosis has since changed (vide infra). Since then, additional histologic variants have been described and more secondary causes have been elucidated. The former included tip, collapsing, and proliferative types, the latter included not only the genetic mutations in podocin and α actinin 4, but this lesion also has been found in association with patients with a congenital single kidney, age-related nephropathy, heroin toxicity, massive obesity, cyanotic heart disease, bisphosphonate therapy, and human immunodeficiency virus nephropathy.

NATURAL HISTORY

Approximately 70% of children and 50% of adults present with clinical feature of the nephrotic syndrome and most of the remainder will develop those features over time. There is some difficulty in determining the natural history of FSGS, particularly in children. The most common approach to the nephrotic syndrome in children is to treat first with daily prednisone therapy and, only if the patient fails to respond, proceed to a renal biopsy examination. In adults there is a tendency to perform a biopsy procedure on the proteinuric patient first and then proceed to therapy. When we compared the outcome in children versus adults we found the only difference was the percentage of FSGS patients presenting with nephrotic syndrome was higher in children. Even this difference tended to equalize over time with fully 89% of children and 82% of adults developing nephrotic range proteinuria during the course of their illness. The groups were equal at presentation in terms of hematuria (32% versus 29%), hypertension (40% versus 35%), and creatinine clearance corrected for body mass (84 versus 90 mL/min). During an average observation period of 11 years a similar percent reached end-stage renal disease (34% versus 32%), chronic renal insufficiency (11% versus 13%), and had persistent proteinuria (13% versus 24%) as well.[34] Studies that have focused on children alone,[35] or adults alone,[36] have reported similar presenting features. In a recent report of 39 children the medium age was 10, sex incidence equal, 80% had hematuria, 21% hypertension, 100% had nephrotic syndrome, and 20% had chronic renal insufficiency at presentation. In all age groups it has been persistence of the nephrotic syndrome that is associated most strongly with renal disease progression.

SPECIFIC THERAPY

There is no known algorithm that predicts accurately which patients should be monitored and treated by conservative therapy alone. However, as opposed to MGN the incidence of spontaneous complete remission is extremely low, in the range of 5%. One area in which conservative treatment alone is suggested is in the patient with nonnephrotic range proteinuria. In most studies in patients with low levels of proteinuria (<2 g/d), the incidence of progression over years is in the range of 10% to 15% versus the 50% to 60% seen in the nephrotic range group. It is important to not include those who have chronic renal insufficiency associated with nonnephrotic proteinuria because their proteinuria probably reflects a low filtering capacity rather than less severe disease.

Table 4. FSGS-Prednisone

Author (Level)	Treatment	Results
Cattran 1998 (4)[34]	P Rx for 2-50/12	CR 42% PR 8%*
n = 93	Response time ≤6/12	CRF 50% in NR/N Rx at 11/1
Rydel, 1995 (4)[36]	P Rx 2-10/12	CR 33%, PR 16%
n = 81	Response time ≤6/12	CRF 50% in NR/N Rx NNS-ESRD† 10%
Ponticelli 1999 (4)[38]	P Rx 2-24/12	CR 36%, PR 16%
n = 53	Response time 6 ± 4/12	CRF 65% in NR at 7/1

Abbreviations: P, prednisone; CRF, chronic renal failure.
* No response/no treatment.
† Nonnephrotic syndrome.

CORTICOSTEROID TREATMENT

All evidence in regards to corticosteroid treatment in FSGS is from case series (level 4). Results in children suggest steroid resistance in biopsy examination–proven FSGS cases may be as high as 60%. There is, however, a marked selection bias in this group because virtually all nephrotic children are treated first with prednisone and only undergo a biopsy examination if resistant, thus steroid-sensitive FSGS cases are never histologically confirmed. The percent labeled resistant also is dependent on the individual study's definition of steroid resistance (ie, how long and the total dosage of corticosteroid), as well as their response definition (ie, complete versus partial remission of proteinuria). It is the highest, for example, when extensive treatment is given including pulse methylprednisolone, long-term prednisone, plus cytotoxic therapy.[37] In adults a similar spread in response rate is seen related to total prednisone exposure. We and others have found similar results in children and in the adults treated in regards to response rate (44% adults, 47% children) as described in Table 4.[34,36,38] In both age groups the average dose in the responsive patients was 80 to 90 mg/kg/d (range, 30−430). The dose/duration to response time in both age groups was significantly greater than that required for minimal change disease treatment.

Tune et al[37] has used the highest published prednisone dose in children with this disorder. Their total dose approximates 470 mg/kg/d over 10 weeks and over 1,000 mg/kg over 18 months of treatment. In a small series, they reported a complete remission rate in 65% but delayed growth, hypertension, and cataracts did occur with this routine (level 5).

CYTOTOXIC THERAPY

The effects of cytotoxic therapy in FSGS and their level of evidence are presented in Table 5.

Table 5. FSGS-Cytotoxics

Author (Level)	Treatment	Results
Tarshish 1996 (2)[39]	CyP 12/52	CR (25%), PR (25%)
n = 60	+ P 40 mg qod 1/1 vs P 1/1	and CRF = at 3.5/1
Turfo-McReddie 1992 (5)[41]	CyP 2 mg/kg	CR, PR (58%)
n = 19	× 10-20/52	CRF (31%) at 6/1 Relapse 88%
Tune 1995 (5)[37]	MP* (30 mg/kg) × 30	CR (66%) PR (9%)
n = 32	+ P 2 mg/kg qod taper over 18/12 + CyP 2 mg/kg 10/52	CRF (25%) at 4-7/1

Abbreviations: CyP, cyclophosphamide; CRF, chronic renal failure.
* Pulse methylprednisolone.

Table 6. Cyclosporine Trials in Adults and Children With FSGS

Author	Level of Evidence	Previous Corticosteroid Duration (wk)	Number CSA Treated	Dose mg/kg/d Duration mo	Remission % Total/Complete	Relapse %/Time
Adults						
Cattran	1	14	26*	3-4/6	69/12	50/2 y
Ponticelli	3	6	14†	5-6/6-12	57/25	43/2 y
Ittel	6	16	7	3-5/7-91	57/25	100/n/a
Children						
Lieberman	1	4	12	6/6	67/25	n/a
Singh	5	8	42	6-10/2-6	60/60	72/2 y

Abbreviation: n/a, not available.
* Plus pulse methylprednisone and oral prednisone.
† Mixed age.

A major issue in the interpretation of the literature in response to cytotoxic agent is the variation in the definition of steroid resistance. The difficulty is compounded by the now recognized variations in histologic type plus that the dose and duration of cytotoxic therapy has been variable. There has been only one randomized clinical trial (RCT) published. The publication year was 1996 but the trial was performed in the 1970s.[39] Their inception cohort was childhood FSGS cases resistant to 8 weeks of prednisone. There were 60 patients in the study and they compared 12 months of treatment in patients randomized with prednisone 40 mg/m^2 on alternate days versus the same prednisone dose plus cyclophosphamide 2.5 mg/kg/d for 90 days. They found no difference at the time of final evaluation in proteinuria, complete remission (CR) 28% versus 25%, decreased proteinuria 25% versus 28%, unchanged or increased proteinuria 43% versus 50%. The end point in regards to renal function was a 30% increase in serum creatinine level. This was also equal, 36% prednisone alone group versus 57% with combined therapy. In the study by Tune et al[37] with the highest remission rate (partial plus complete), 78% (25 of 32) of their children required alkylating agents in addition to high-dose corticosteroids. In contrast, Waldo et al[40] by using a similar routine found 80% (8 of 10) had progressive renal failure. The Argentina experience was more positive with prolonged cyclophosphamide but the relapse rate was very high.[41] In comparison, Martinelli et al[35] recently reported a small number of steroid-resistant children treated with 12 weeks of cyclophosphamide with only a 22% response rate defined as either complete or partial remission (all these studies level 5).

The studies in adults using cytotoxic therapy are of poor quality. There have been no randomized or long-term prospective observational data with cytotoxic therapy alone. The largest and best described was by Ponticelli et al.[38] Forty percent (27 of 65) had a remission, (CR 11%, partial remission [PR] 29%) with cytotoxics as first-line therapy. In the steroid-resistant group (n = 11), remission was 55% (CR 9%, PR 45%). However, all patients had prolonged cyclophosphamide and/or azathioprine therapy averaging 40 ± 25 weeks of treatment. The cyclophosphamide dose averaged 1 mg/kg or a total exposure of 280 mg/kg, well into the toxicity range.

In summary, the support for the use of the currently acceptable short course of 12 to 16 weeks of cytotoxic therapy in steroid-resistant FSGS cases in both children and adults is poor, with an expected response rate of no more than 20% even combining partial and complete remission rates (level 5). Side effects are likely to be significant with a more prolonged course of cytotoxic therapy, including an increased incidence of bone marrow toxicity, infertility, infection, and late risk for cancer.

CYCLOSPORINE THERAPY

A summary of the best studies on the use of cyclosporine in FSGS is outlined in Table 6. The same issue exists in regards to the definition used for steroid resistance. We have included a column in this table so the corticosteroids pretreatment time can be assessed.

There is only one level 1 study in adults with steroid-resistant FSGS.[42] It compared 6 months of cyclosporine with 6 months of placebo with all

patients receiving low-dose prednisone at 0.15 mg/kg/d. Although the entry requirement was a minimum of 8 weeks of prednisone, the actual drug exposure was between 100 and 120 mg/kg/d and the mean duration of treatment was 14 weeks in both groups. At the end of treatment 69% of the cyclosporine patients were in remission (CR 12%, PR 57%) versus 4% partial remission in the placebo group. The time to remission ranged between 1 and 15 weeks. The relapse rate was substantial with a 40% relapse rate within 52 weeks. However, 18 months posttreatment fully 50% of the initial responders remained in remission. This response rate is similar to the other adult series (Table 5), but the other trials were less rigorous with lower evidence ratings. In the study by Ponticelli et al,[43] 57% of those treated had a remission and approximately 40% remained in remission at 2 years follow-up but the details separating the outcome in their FSGS versus minimal change disease patients were incomplete. The study by Meyrier et al[44] needs special comment. Although there were 112 adult patients treated with cyclosporine, they were a mixture of both steroid-resistant and steroid-dependant cases and minimal change disease and FSGS patients. In the 27 patients with biopsy examination–proven FSGS only one-third responded but there was a paucity of clinical pathologic correlation given by the researchers (level 5).

In children only the RCT by Lieberman et al[44a] fulfilled the criteria for level one evidence. Pretreatment was a standard 4 weeks of prednisone at 60 mg/m^2. At entry glomerular filtration rate was greater than 30 mL/min and the patient had to have persistent proteinuria. At the end of 6 months of cyclosporine therapy, 66% of patients had a remission (25% CR) compared with no significant change in the protein/creatinine ratio in the placebo group. Unfortunately, there was no follow-up evaluation in terms of relapse rate or effects on renal function beyond 6 months of treatment. All the other studies in children are level 5. On average, these patients were treated with 5 to 8 mg/kg/d of cyclosporine for between 3 and 36 months, with the response rate averaging 70%. Approximately half the responders had a complete remission and half a partial remission. The question of nephrotoxicity versus benefit of therapy with cyclosporine remains a constant area of debate. Nephrotoxicity has been shown clearly in solid organ transplantation most notably in the early heart transplant series. However, the cyclosporine dose ranged between 10 and 20 mg/kg/d for prolonged periods in these studies. Most studies in nonrenal diseases including patients with psoriasis and uveitis have shown nephrotoxicity but the changes were mild and dose dependent. It generally is accepted that therapy for up to 1 year using a cyclosporine dose of less than 5 mg/kg/d is unlikely to produce serious nephrotoxicity.

There is only one study that suggested renal preservation was maintained in FSGS patients with cyclosporine usage. At the end of 4 years of follow-up in the study by Cattran et al[42] over 50% of the placebo group versus only 25% of the cyclosporine-treated patients had halved their renal function as measured by creatinine clearance ($P < .05$).

OTHER THERAPIES

MMF has been used only in pilot studies in FSGS. In a report by Choi et al,[29] 18 of their 46 patients treated with MMF had FSGS as their primary disease. Approximately half these patients were nephrotic and two-thirds had some degree of chronic renal insufficiency. This was a mixture of steroid-resistant and steroid-dependent patients but it did include some with documented progressive renal insufficiency. A marked improvement was seen with MMF treatment in the urine protein to creatinine ratio after a variable amount of time ranging from 4 to 13 months. No patents had deterioration in their serum creatinine during treatment. The majority of patients with previous renal insufficiency remained stable during follow-up periods ranging from 4 to 12 months (level 5). Another new approach to therapy is pentoxifylline, a small molecule felt to act as an antagonist to tumor necrosis factor α and to be an antifibrotic agent in animals. A recent pilot study using this drug showed slowing in the rate of renal deterioration but surprisingly there was no change in proteinuria (level 6).

One of the most controversial areas is the use of plasma exchange or plasmapheresis in patients with FSGS. In a number of small uncontrolled trials with recurrent FSGS posttransplant, renal function stabilized and proteinuria reversed in approximately 50% of the patients. In native kidney disease, however, the results were not nearly as positive. Certainly when used as a single agent there is little indication of long-term improvement. A report by Mitwalli[45] indicated that with pro-

longed plasma exchange (17 courses of treatment over 6 mo) plus both pre- and posttreatment with prednisone and cyclophosphamide, they were able to achieve complete remission in 6 of 11 patients, partial remission in 2 of 11, and no response in only 3 patients. At 2 years of follow-up approximately half of the patients had relapsed or gone on to end-stage renal failure.

IgA NEPHROPATHY

IgA nephropathy is now the most common primary histologic diagnosis found on routine renal biopsy examination. It is uncommon in children, rare in blacks, and there is a significant family history in 10% to 20% of cases. The natural history is quite variable. Although originally this was attributed to geographic or genetic factors, recent data suggests most of the outcome variation is owing to lead-time bias related to population screening protocols versus symptom-driven evaluations. The overall prognosis is favorable with up to 70% to 80% 10-year renal survival in countries with screening programs. In contrast in Canada where patients undergo a biopsy examination largely based on symptoms, up to 50% of the patients had renal disease progression within 5 years.[46,47] This marked variation in natural history emphasizes the need for a prognostic algorithm before committing the patient to potentially dangerous treatment. Hypertension, moderate proteinuria (1–4 g/d), and renal insufficiency at onset are independent factors that indicate a poor prognosis but these are qualitative measurements and have poor specificity. A recent evaluation of almost 300 cases from our registry indicated by univariate linear regression that mean arterial pressure over time, initial proteinuria, and proteinuria over time, as well as Lee grade V histologic changes were the only 4 predicators of outcome. A subsequent multivariate analysis indicated only mean proteinuria over time and mean arterial pressure over time were independent factors related to progression.[47] This model has not yet been validated.

SPECIFIC THERAPIES

Corticosteroids

A randomized controlled study by Pozzi et al[48] compared pulse methylprednisolone 1 g/d for 3 consecutive days at the beginning of months 1, 3, and 5 plus oral prednisone 0.5 mg/kg on alternate days for 6 months with supportive therapy alone in 86 consecutive patients with IgA nephropathy (level 1). Proteinuria was reduced by almost 50% in the steroid group from 2 g/d to 1 g/d by 6 months with no significant change in the control group. This reduction in the proteinuria persisted for up to 4 years. There was also a significant slowing of progression with 9 of 43 patients in the steroid group versus 14 of 43 in the control group reaching the primary end point of a 50% increase in plasma creatinine by 5 years ($P < .048$). Factors influencing renal survival were steroid treatment, sex (men progressed faster), and degree of vascular sclerosis on biopsy examination. In another study by Kobayashi et al[49] steroid treatment was compared with a contemporary cohort. They found an 80% survival in the steroid-treated group versus only 34% in the untreated group after 10 years ($P < .001$). Patients with only mild histologic changes or decreased renal function at entry showed no benefit with treatment in the final analysis (level 4) Two other shorter but randomized controlled trials with steroids given for 4 and 3 months showed no benefit in patients with IgA nephropathy,[50,51] suggesting the need for larger numbers and/or more prolonged duration of therapy (level 2).

Corticosteroids Plus Cytotoxic Agents

There is one RCT by Ballardie and Roberts[52] who compared prednisolone 40 mg/d reduced to 10 mg/d by 2 years plus cyclophosphamide 1.5 mg/kg/d for the first 3 months then azathioprine at the same dose for 2 years compared with a control group with no immunosuppression. At entry all patients had to have impaired renal function (>130 umol/L) as well as declining renal function, documented by a serum creatinine increase of at least 15% in the prior year. An important exclusion criterion was patients with a serum creatinine level greater than 250 umol/L. Cumulative renal survival after 2 years was improved significantly with treatment ($P < .005$). This was paralleled by a significant, 4-fold slowing in the rate of deterioration in renal function in the treatment group (level 1). The mean protein excretion was slightly higher in the control group than the treatment group at entry (4.6 versus 3.9 g/d) but the change in proteinuria by 12 months was significantly greater in the treatment group (delta 2.1 g/d) versus control (delta 0.2 g/d) This improvement in proteinuria was maintained

throughout the 3 years of follow-up evaluation ($P < .02$). Arterial pressure did not differ between groups. In a recent pediatric study of IgA nephropathy, patients were assigned randomly to a combination of prednisolone, azathioprine, heparin, warfarin, and dipyridamole (N = 40) compared with heparin, warfarin, and dipyridamole alone (N = 38) The investigators noted that the combined therapy group after 2 years showed a significantly greater reduction in urine protein excretion ($P < .001$) although no difference in creatinine clearance. The great majority of patients had repeat renal biopsy examination and the combined therapy group showed no increase in segmental or global glomerulosclerosis compared with an increase from 3.9% to 16% in the nonsteroid/cytotoxic group. This was accompanied by a quantitative reduction in the extent of the mesangial IgA deposits in the combined therapy group (level 1). A smaller nonrandomized trial (N = 20) compared a short, 2-month course of pulse plus oral steroid plus cyclophosphamide with controls and showed a marked benefit on 5-year renal survival. This was presumably owing to the acute anti-inflammatory effects of the drugs, given the limited duration of the treatment (level 3).[53]

Fish Oil Supplements

Hamazaki[53a] in 1984 first reported that omega 3 fatty acids in the form of fish oil preserved renal function in individuals with immunoglobulin A nephropathy. The omega 3 fatty acids are substrates for fatty acids of the α linolenic series and their consumption shifts eicosinoids from the linolenic series to the α linolenic series. The omega 3 fatty acids compete with achadonic acid to produce trienoic eicosanoids, which may slow renal disease progression by a variety of pathways such as reducing glomerular and interstitial inflammation, mesangial cell contractility, platelet aggregation, and vasoconstriction. In an RCT trial by Donadio et al,[54] patients with IgA nephropathy were assigned randomly to receive either fish oil supplement 12 g/d (N = 55) or placebo composed of olive oil (N = 51). Entry criteria included biopsy examination–proven IgA nephropathy, urine protein excretion greater than 1 g/d, or a serum creatinine concentration increase by 25% during the preceding 6 months. Exclusion criteria were a serum creatinine level of 3 mg/dL or greater and an expected renal survival of less than 2 years. All patients with hypertension were treated with the ACE inhibitor enalapril. The primary study end point was loss of renal function defined as 50% increase or greater in serum creatinine concentration during the 2 years of treatment. In the fish oil supplement group, 6% reached this end point compared with 33% in the placebo group ($P = .002$). The median annual change in the serum creatinine concentration was 0.03 mg/dL in the fish oil supplement group versus 0.14 mg/dL in the placebo group ($P = .001$). The cumulative percentage of patients who died or reached end-stage renal disease was 10% in the fish oil supplement group after 4 years versus 40% in the placebo group ($P = .006$). Proteinuria was reduced modestly in both groups but was not significantly different between the placebo and the control group (level 1). The long-term outcome of patients in this IgA nephropathy study was reviewed in a subsequent article using the same primary end point. After a mean of 6.4 years a significantly greater number of the placebo patients reached this point and had gone on to end-stage renal disease ($P = .003$) (level 3). A third study by the same group[55] compared their previous fish oil supplement dose with a double-dose regime. All the patients had some degree of renal insufficiency. The primary end point was within patient rates of change in serum creatinine over a minimum of 2 years of treatment. This showed no difference with an annualized median change in serum creatinine level of 0.08 mg/dL in the standard dose group versus 0.1 mg/dL in the high-dose group ($P = .5$). Patient compliance was excellent and no adverse events were noted. (level 1). There has been, however, 2 other fish oil supplement treatment RCTs[56,57] with smaller numbers but similar doses of the eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) that showed no benefit. In a meta-analysis Dillon,[58] using statistical methods that adjusted for variations in follow-up, entry criteria, and sample size calculations, indicated the mean effect was not significant for fish oil supplementation in IgA nephropathy but the probability of a minor beneficial effect was 75%.

ACE Inhibitors

ACE inhibitor therapy has been suggested to have benefits beyond lowering blood pressure. A specific renal protective function has been seen in prospective studies of nondiabetic proteinuric con-

ditions and in a retrospective study of patients with IgA nephropathy.[59] The latter compared a normotensive IgA population with 2 hypertensive IgA populations, one treated with ACE inhibitors and the second with other antihypertensive agents. The median slope of creatinine clearance over an observation period up to 24 months indicated a significant benefit beyond blood pressure control in the ACE-treated patients compared with the other agents hypertensive group ($P < .007$) (level 3).

NEW THERAPIES

MMF

A recent randomized controlled trial from China published in abstract form had 62 patients with proteinuria greater than 2 g/d and serum creatinine levels less than 350 umol/L randomized to either MMF 1.0 to 1.5 g/d (n = 31) or to prednisone 0.8 mg/kg/d (N = 31). After 3 months of therapy there was a significantly greater improvement in the MMF-treated group in terms of both decreased proteinuria and improved plasma albumin level ($P < .01$). The greater reduction in proteinuria remained at the end of 12 and 18 months ($P < .05$). Significant side effects were seen in 5 of the MMF-treated patients including diarrhea (3), herpes zoster (1), and nausea (1), but all abated without drug withdrawal. There was no difference in renal function over the follow-up period (level 2).

Management Strategy

A distinct adverse profile for patients with IgA nephropathy is not established as clearly and no predictive algorithm has yet been validated as in MGN. However, in general, at presentation adverse factors include renal insufficiency, hypertension, and proteinuria greater than 0.5 g/d. Persistent proteinuria and hypertension despite therapy also portend a poor prognosis. In the group without an adverse profile, ACE inhibitor therapy, ideal blood pressure control, as well as other conservative therapies to reduce proteinuria are sufficient (grade C). If at onset or if adverse factors develop over time, idealization of the blood pressure and the use of ACE inhibitor therapy should be maintained plus the introduction of prednisone plus a cytotoxic agent for a 1- to 2-year period (grade A). Alternate (or additional) therapy should be fish oil supplementation (grade A). Deteriorating renal function should trigger either the addition or replacement of one of the earlier-described regimens with the alternate approach (grade B) or a change to MMF therapy (grade C).

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