Glomerular disease: why is there a dearth of high quality clinical trials?

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There is a paucity of high quality clinical trials in glomerular disease, particularly in non-diabetic kidney disease. The aims of this review include quantifying the extent of this problem and exploring reasons for the scarcity of such trials in primary glomerular disease, with an emphasis on immunoglobulin A nephropathy, minimal change disease, focal segmental glomerulosclerosis, and membranous nephropathy in comparison with the more common diseases of diabetic nephropathy and lupus nephritis. Reasons for the dearth of high quality clinical trials in primary glomerular disease include (1) low prevalence of disease; (2) variability in clinical presentation; (3) variability in treatment response; (4) lack of consensus in definitions; (5) difficulty in recruiting patients; (6) high costs of randomized controlled trials; and (7) lack of collaborative efforts. To facilitate greater numbers of high quality clinical trials in glomerular disease, practice guidelines should establish common classification systems of disease and common clinical end points, industry and non-industry sponsored research should find common ground and work together toward advancing science, and national registries should be created to encourage collaborations across institutions and across nations.

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Glomerular disease is an important cause of morbidity and mortality;[1,2] however, with the exception of diabetic nephropathy (DN) there has been a paucity of high quality randomized controlled trials (RCTs) in this area. The aims of this review include quantifying the extent of this problem and exploring reasons for the scarcity of such trials in glomerular disease. As all etiologies of glomerular disease could not be reviewed, the following major glomerular disease entities were chosen as representative: DN, lupus nephritis (LN), immunoglobulin A nephropathy (IgAN), minimal change disease (MCD), focal segmental glomerulosclerosis (FSGS), and membranous nephropathy (MN).

CHARACTERISTICS OF PUBLISHED CLINICAL TRIALS IN GLOMERULAR DISEASE

Medline and the Cochrane Database were searched for articles written in English and published between 1990 and 2009 using the following keywords: (1) diabetic nephropathy; diabetic kidney disease; (2) lupus nephritis; lupus nephropathy; lupus glomerulonephritis; (3) Immunoglobulin A nephropathy; immunoglobulin A nephritis; immunoglobulin A glomerulonephritis; immunoglobulin A nephropathy; (4) minimal change disease; minimal change nephrotic syndrome; lipoid nephrosis; (5) focal segmental glomerulosclerosis; (6) membranous nephropathy; membranous glomerular nephropathy; membranous glomerulonephritis. Additional criteria used to select articles included the following: (1) articles must have been RCTs or meta-analyses; (2) *post-hoc* analyses of RCTs were only included if they evaluated different end points than the original study; (3) only studies involving human subjects were included; and (4) studies which included patients with heterogeneous etiologies of kidney disease were counted under each individual category, assuming that the category included a sample size of at least 10 patients. Among the studies in which the total enrollment was fewer than 10 patients, designation was attributed solely to the category with the greatest number of patients.

Using the above criteria, the number of RCTs and meta-analyses investigating DN, LN, IgAN, MCD, FSGS, and MN were determined (Figure 1; Supplementary Information for complete list of studies). As shown, many RCTs and meta-analyses have been published regarding DN, however, there is a dearth of studies evaluating non-diabetic glomerular disease.

Table 1 shows the total number of patients enrolled and the mean duration of follow-up (not including washout or run-in periods) for each of the RCTs. The average number of subjects enrolled in trials of DN far outweighs the number enrolled in trials of the other glomerular diseases. The average duration of follow-up is comparable across all six diseases represented.

In addition to the relatively small sample sizes and general shortage of RCTs evaluating non-diabetic glomerular disease, the quality of many of these trials was poor. For example, a meta-analysis of 10 RCTs investigating treatments for IgAN found that none adequately described appropriate randomization methods, only 2 of 10 had blinding of both participants and investigators, 5 of 10 reported intention-to-treat analysis, and 6 of 10 had relevant number of patients lost at follow-up.[3] Furthermore, pertinent data was often missing from methods and statistical sections. Similarly, in a meta-analysis of 18 RCTs investigating immunosuppressive treatment for idiopathic MN, few of the conducted trials included information on the method of randomization, reported on blinding of both investigators and participants, used intention-to-treat analysis, or provided information regarding completeness of follow-up.[4]

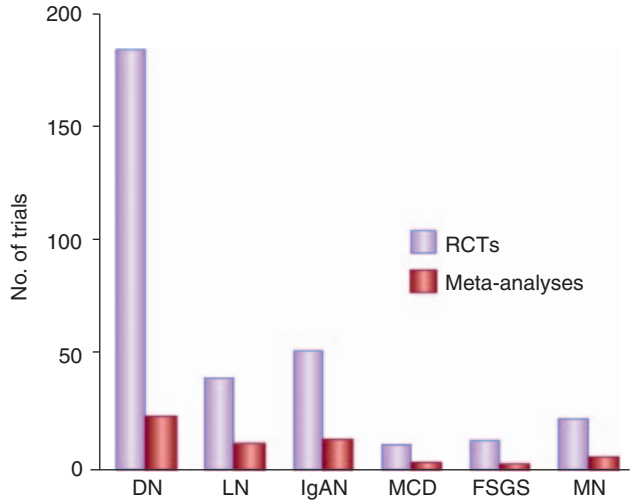

Figure 1 | Number of RCTs and meta-analyses, by renal disease category. DN, diabetic nephropathy; FSGS, focal segmental glomerulosclerosis; IgAN, immunoglobulin A nephropathy; LN, lupus nephritis; MCD, minimal change disease; MN, membranous nephropathy; RCT, randomized controlled trial.

WHY THE PAUCITY OF CLINICAL TRIALS IN GLOMERULAR DISEASE?

Low prevalence of disease

One obvious explanation for the scarcity of RCTs in non-diabetic glomerular disease relates to their infrequent occurrence. Table 1 shows estimates of the incidence of DN, LN, IgAN, MCD, FSGS, and MN. The incidence of DN is approximately 20-fold the incidence of LN and over 40-fold the incidence of the primary glomerular diseases. Studies of non-diabetic renal disease limited to a single center or few centers would be unlikely to recruit adequate number of patients in any reasonable time period.

However, rarity alone does not fully explain the scarcity of RCTs in glomerular disease. By comparison, Huntington's disease and Guillain–Barre syndrome are the two rare neurological disorders with estimated incidences of 0.3 and 1.3 per 100,000 people per year, respectively, which is similar to the incidence of the primary glomerular diseases.[5,6] However, the number of RCTs performed in the last two decades, evaluating these two disorders, is 40 and 30, respectively, which is substantially greater than the corresponding number of trials evaluating the primary glomerular diseases (with the exception of IgAN). Accordingly, alternative explanations for the scarcity of RCTs addressing glomerular disease must be sought.

Variability in clinical presentation, decision to biopsy, and decision to initiate therapy

Many primary glomerular diseases are heterogeneous in their clinical presentation. Some patients present with a gradual asymptomatic increase in proteinuria, while other patients present with the sudden onset of massive edema and overt nephrotic syndrome. Even among patients with the same type of glomerular histopathology, the degree of proteinuria may vary and the threshold for starting immunosuppressive therapy is often controversial. In MN, for example, rates of spontaneous remission are very high and many patients may

Table 1 | Number of subjects enrolled (*n*) and duration of follow-up (weeks) for RCTs, and incidence (cases/100,000/year)[46–50] of renal disease

	n	Follow-up (weeks)	Estimated incidence (cases/100,000/year)
Overall	104.2 ± 13.4	79.9 ± 5.7	NA
Diabetic nephropathy (DN)	127.6 ± 19.3	70.0 ± 6.1	54
Lupus nephritis (LN)	68.7 ± 12.2	106.2 ± 17.3	2.8
IgA nephropathy (IgAN)	51.9 ± 4.7	113.3 ± 16.7	1.4
Minimal change disease (MCD)	34.7 ± 5.2	83.1 ± 25.0	0.5
Focal segmental glomerulosclerosis (FSGS)	34.9 ± 5.2	62.7 ± 18.8	1.1
Membranous nephropathy (MN)	49.4 ± 6.0	123.8 ± 29.8	0.7

Abbreviations: NA, not applicable; RCT, randomized controlled trial.
Values indicate mean ± s.e.m.

receive unnecessary treatment. One prospective study of 100 patients with idiopathic MN, who received symptomatic therapy only (i.e. no glucocorticoid or immunosuppressive drugs), found an 88% estimated probability of retaining adequate kidney function at 5 years, and 65% of patients had complete or partial remission of proteinuria.[7] In contrast, other investigators recommend a wait-and-see policy in idiopathic MN only for low-risk patients.[8,9] Even in these studies, the indication for immunosuppressive therapy differs between persistent proteinuria[8] and risk-stratifying patients based on the renal function and urinary excretion of β2-microglobulin.[9] Similarly, controversy exists regarding the optimal timing of renal biopsy. In IgAN, for example, some experts advocate for early biopsy in patients with persistent microhematuria and low-grade proteinuria, whereas others advocate an initial trial of angiotensin converting enzyme inhibitor therapy, limiting renal biopsy only to those patients with a non-satisfactory antiproteinuric response. Such heterogeneity of disease activity and the difference in opinion of when to perform biopsy and when to initiate specific therapy present a challenge to investigators.

Variability in treatment response

An additional challenge to investigators studying glomerular disease is heterogeneity of response to the treatment. IgAN, for example, may have a variable response to treatment depending on the ethnicity and inclusion criteria of study participants. Although a recent meta-analysis concluded that the current available evidence does not support the routine use of mycophenolate mofetil (MMF) in patients with IgAN,[10] this finding was based on only four RCTs. Among these four RCTs, the two which included predominantly the Asian patients[11,12] found a significant reduction in proteinuria with MMF, whereas the two that included caucasian[13] and north European patients[14] found no reduction in proteinuria compared with controls. Similarly, although a meta-analysis[3] concluded that cytotoxic agents (cyclophosphamide and azathioprine) are beneficial in IgAN, this finding was driven almost entirely by a single positive study[15] in which the inclusion criteria differed significantly from other studies that have explored this treatment modality. Specifically, the patients in Ballardie's study were older, had higher levels of serum creatinine, and had more severe renal lesions on biopsy, as compared with other trials of cytotoxic agents on patients with IgAN.[16–18]

Lack of consensus in definitions

Not only are both clinical presentation and response to treatment highly variable in many glomerular diseases but the spectrum of histopathology on renal biopsy may also be diverse. Disagreement regarding histopathological classification within a given disease entity is not uncommon. This concept is well-exemplified by FSGS, in which a classification system of five distinct variants has been proposed and widely accepted.[19] However, as noted by Meyrier,[20,21] this system is not without limitations as one renal biopsy may reveal multiple variants simultaneously or, alternatively, may indicate a different histological variant due to sampling error. Others have proposed that the classification of primary nephrotic diseases should incorporate specific pathophysiological mechanisms.[22]

Further disagreement regarding disease categorization centers around lumping and splitting. For example, some investigators[23] favor grouping tip variant FSGS as being merely a variant of MCD. Other investigators have suggested that MCD itself encompasses a heterogeneous group of disorders and can be split into three distinct categories on the basis of the presence or absence of hypoalbuminemia, overt edema, and hypovolemia.[24] This problem is further complicated in children with nephrotic syndrome, wherein a renal biopsy is typically not performed before initiating corticosteroids. Moreover, in some diseases, such as MN, the ability of the renal histopathology to predict disease progression and response to therapy is still debated.

The recognition of problems associated with the lack of uniform and widely accepted histopathological classification systems has been addressed by collaborative formulations in a number of glomerular diseases, including LN,[25] FSGS,[19] and, most recently, IgAN. Specifically, with regard to IgAN, lack of consensus regarding its pathological classification was addressed by the Working Group of the International Nephropathy Network and the Renal Pathology Society.[26] Renal biopsies from 265 adults and children with IgAN were examined, and four specific pathological features were identified as having an independent value in predicting the renal outcome. In LN and FSGS, validation of these classifications has been made in other populations. This remains to be done in IgAN. It should be emphasized, however, that one of the unique characteristics of the IgAN classification scheme is that the pathological features identified had significant predictive value even after accounting for all clinical indicators available at baseline, thereby potentially becoming relevant factors in future study designs. Hopefully, greater consensus in definition, including agreement on classification systems as well as important clinical end points, will encourage more robust collaborative efforts (see below) and will allow for greater number of high quality clinical trials.

Difficulty in recruiting patients

Many clinical trials investigating primary glomerular disease use medications with narrow therapeutic indexes and relatively high rates of toxicity, such as immunosuppressant and immunomodulatory agents. Thus, it is likely that patients may have greater reluctance to participate in such trials as compared with trials of milder interventions, such as angiotensin converting enzyme inhibitors in DN. Furthermore, patients may be especially reluctant to participate in trials, such as those studying primary glomerular disease, in which the response to treatment is highly variable. This notion is especially true for diseases, such as IgAN and MN, which often have a slow progressive course. In addition, many patients as well as

their physicians may feel it is better for an individual patient not to enter a controlled trial but rather to wait and see the results of such studies in other patients. Finally, those patients who are most likely to progress in any given disease will be reluctant to accept a placebo arm to any study given the wide array of potential immune modulating agents available, which are Food and Drug Administration (FDA) approved (albeit for other indications).

Another major barrier to patient recruitment relates to late diagnosis and late referral to a nephrologist. Earlier referral of patients by general practitioners would greatly increase the pool of potential subjects for enrollment in prospective clinical trials. Moreover, there is increasing evidence that early referral to a nephrologist, defined by some as greater than a year before the initiation of dialysis, results in improved patient survival.[27,28] For this reason, many have advocated for more intensified education of non-nephrologist physicians regarding the importance of early referral to a specialist.[29] Although these studies predominantly involved referrals for end-stage renal disease evaluation among predialysis patients, it is not unreasonable to extrapolate these findings to glomerular disease and to expect improved outcomes with earlier referral here as well.

High costs of RCTs

The increasing costs associated with performing RCTs is, without a doubt, a major barrier. According to one report,[30] the cost per patient for performing Phase 1, 2, and 3 clinical trials in 2006 was $15,700, $19,300, and over $26,000, respectively, and these costs continue to increase. For example, the European clinical trials market in 2008 was calculated to have a value of $32 billion, and is projected to reach a value of $47 billion by 2012.[31] Reasons for the increasing costs associated with RCTs are numerous and include expenditures related to: (1) salaries of research staff, including study coordinators, research pharmacists, and administrators; (2) complex statistical methodology requiring expensive data management systems and highly-trained statisticians (often at the PhD level); (3) increased documentation requirements; (4) independent data safety and monitoring committees; (5) institutional review boards; and (6) compliance with federal regulations, such as the Health Insurance Portability and Accountability Act, making the sharing of data both complex and expensive.[32] Although these costs and the problems associated with them are not unique to nephrology, they are particularly challenging to our field because of the limited funding of our national granting agencies as compared with certain other fields.

Such prohibitive costs are one reason that large RCTs can sometimes only be supported by pharmaceutical companies or governmental funding agencies such as the NIH (National Institutes of Health). Clearly the aim of industry-sponsored trials is to bring a new drug to market or to broaden the indication of an existing drug. For example, the 'gold standard' medication for the treatment of LN for years was intravenous cyclophosphamide, supported by data derived from NIH 'in-house' studies. This medication never received an FDA indication as therapy for LN. Thus, to get the FDA approval for a new medication for LN, the new drug requires evidence of superiority, not equivalency, to intravenous cyclophosphamide. Pharmaceutical studies, designed to obtain the FDA approval, must therefore adjust recruitment and duration for the end point of superiority rather than the easier aim of equivalency. Hence, the pharmaceutical-sponsored aspreva lupus management study trial of MMF versus intravenous cyclophosphamide needed to recruit 370 patients to attempt to establish the superiority of the former over the latter regimen, and thereby broaden the indication of MMF.[33] In contrast, the Euro–Lupus group, funded by a non-industry source (the European League Against Rheumatism), was able to show equivalency of two different regimens of cyclophosphamide with only 90 patients.[34] For generic drugs, funding a large study essentially means that, with rare exceptions, a governmental agency has to provide the funding, as pharmaceutical companies have little incentive to study and fine-tune optimal dosages for medications, which are inexpensive and have already been FDA-approved. An example is the FSGS clinical trial, which compares generic cyclosporine with MMF and steroids in patients with steroid-refractory FSGS.[35]

Lack of collaborative efforts

Finally, among diseases as rare as the primary glomerulopathies, recruiting adequate number of subjects for high quality RCTs is nearly impossible without robust collaborative efforts. Nonetheless, these efforts are lacking. Among the RCTs that evaluated MCD, for example, only 3/11 (27.3%) were multi-center studies (2/9 in children and 1/2 in adults). Consequently, among the six glomerular diseases studied in this review, MCD represents the category with the fewest number of enrolled subjects (Table 1). Furthermore, in cases where single-center designs are used, lengthy recruitment periods are often required and concepts of ideal management may change during this time. Large, multi-center trials with relatively short recruitment periods are much less likely be affected by this problem.

The European Vasculitis Study Group,[36] a partnership of clinicians and researchers interested in clinical trials of vasculitis, represents an ideal model of collaborative efforts spanning across multiple nations. The group has been successful in carrying out several, large RCTs evaluating antineutrophil cytoplasmic-antibodies associated vasculitis, including a study establishing the safety of azathioprine substitution for cyclophosphamide after remission ($n = 155$)[37] and a study establishing the efficacy of plasma exchange in improving rates of renal recovery ($n = 100$).[38] Collaborative efforts such as these should be enthusiastically echoed by similar efforts in the investigation of glomerular disease. Such efforts have been made in treating LN by combined efforts of rheumatology and nephrology recruitment,[33,39,40] however, they are lacking in other areas of glomerular disease.

WHY THE SHORTAGE OF META-ANALYSES IN GLOMERULAR DISEASE?

The most obvious reason for the shortage of meta-analyses among the primary glomerular diseases is the shortage of corresponding RCTs. However, a second factor is also a likely contributor: heterogeneity of clinical end points. Meta-analyses depend on common end points to answer specific clinical questions. When common clinical end points cannot be found, meta-analyses are either not performed or performed using a distribution-based approach, such as Cohen's standardized effect size, which is simply the mean change divided by the s.d.[41] However, this approach has several limitations.[42] Some investigators have suggested that effect sizes may underestimate clinically important differences.[43] Furthermore, effect sizes cannot be used to interpret individual-based differences over time.[44]

Table 2 shows the wide heterogeneity among clinical end points used in RCTs of glomerular disease. Even among the end points of which significance is universally agreed upon, such as proteinuria in the progression of kidney disease, there is variability among studies regarding methods of quantification and thresholds of clinical relevance. Despite the heterogeneity of clinical end points, the focus of clinical trials in glomerular disease often centers largely on proteinuria and/or serum creatinine. End points such as quality of life have been slow to be embraced, especially as compared with other nephrology subspecialties such as anemia of chronic kidney disease where an abundance of literature exists on quality of life.[42]

Table 2 | Heterogeneity of clinical end points used in RCTs of renal disease

Composite outcomes	Progression to CKD or death; doubling of baseline serum creatinine or progression to CKD stage IV or V or ESRD
Reduction in GFR	Serum creatinine, eGFR (MDRD, Cockgraft–Gault, iothalamate clearance, creatinine clearance), or (99 m) Tc-diethylenetriamine penta-acetic renogram
Proteinuria	Spot microalbuminuria, spot urine protein/creatinine; 24 h urine protein collection
Remission	Complete/partial: improvement in proteinuria, improvement/stabilization of renal function, and improvement/stabilization of systemic features.
Blood pressure (BP) control	Ambulatory BP, office BP, nocturnal BP, orthostatic hypotension, number of antihypertensive medications
Glycemic control	Fasting blood glucose, hemoglobin A1c, and serum insulin and C-peptide concentrations
Lipid profile	Low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglycerides (TGs), and cholesterol
Biomarkers/serology	Serum TNF-α, IGF-1, *N*-acetyl-β-glucosaminidase, type IV collagen, von Willebrand factor, anti-double-stranded (ds) DNA antibodies; urinary prostaglandin E2, urinary TGF-β
Histological/Pathological	Mesangial fractional volume (Mes/glom), nephrin expression, and urinary podocytes
Health-related quality of life	SF-36, visual analog scale (VAS), and lupus symptom checklist

Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filteration rate; ESRD, end-stage renal disease; GFR, glomerular filteration rate; IGF-1, insulin-like growth factor 1; MDRD, modification of diet in renal disease; RCT, randomized controlled trial; TGF-β, transforming growth factor β; TNF-α, tumor necrosis factor α.

RECOMMENDATIONS

(1) To facilitate greater numbers of high quality clinical trials in glomerular disease, investigators and clinicians should be encouraged to agree on common classification systems of disease and common clinical end points. To this point, a global non-profit foundation known as Kidney Disease: Improving Global Outcomes is currently conducting an evidence-based review process to establish clinical practice guidelines for glomerulonephritis.[45] The guidelines are anticipated to be published in 2011 and will include disease classification definitions and recommendations for future research.

(2) To reconcile the contrasting aims and resources of studies funded by pharmaceutical and non-industry sources, collaboration between these two entities is to be strongly encouraged. The funding provided by the industry would ensure high quality research, with high numbers of enrolled patients and adequate follow-up, whereas peer-review agencies would lend credibility and aid in the recruitment of patients through their connections with national registries (see #3 below).

(3) Finally, given the small number of patients enrolled in most studies of glomerular disease, national registries should be created to facilitate collaborations across institutions and across nations, as modeled by the European Vasculitis Study Group. Such an endeavor would have a greater chance of success if physicians feel a greater obligation to register such patients in a central databank, perhaps with the supervision and monitoring by a governmental agency, thereby emulating various cancer registry models.

In conclusion, until there is greater agreement on classification systems of disease and greater collaboration among investigators, it is unlikely that the fruit on the tree of glomerular knowledge will germinate to its full potential.

DISCLOSURE

All the authors declared no competing interests.

SUPPLEMENTARY MATERIAL

Supplementary material is linked to the online version of the paper at http://www.nature.com/ki

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