Effects of Enalapril versus Placebo as a Treatment for Canine Idiopathic Glomerulonephritis

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A blinded, multicenter, prospective clinical trial assessed the effects of enalapril (EN) versus standard care in dogs with naturally occurring, idiopathic glomerulonephritis (GN). Twenty-nine adult dogs with membranous (n = 16) and membranoproliferative (n = 13) GN were studied. Dogs were randomly assigned to receive either EN (0.5 mg/kg PO q12–24h; n = 16) or placebo (n = 14) for 6 months (1 dog was treated first with the placebo and then with EN). All dogs were treated with low-dose aspirin (0.5–5 mg/kg PO q12–24h) and fed a commercial diet. At baseline, serum creatinine (SrCr), systolic blood pressure (SBP), and glomerular histologic grade were not different between groups, but the urine protein/creatinine ratio (UP/C) was greater in the EN group compared with the placebo group (8.7 ± 4.4 versus 4.7 ± 2.3). After 6 months of treatment, the change in UP/C from baseline was greater in the EN group compared with the placebo group (–4.2 ± 1.4 versus 1.9 ± 0.9 in the placebo group). When data were adjusted for changes in SrCr (SrCr × UP/C) a similar significant reduction was noted (–2.2 ± 15.2 versus 8.4 ± 10.1). The change in SBP after 6 months of treatment also was significantly different between groups (EN = –12.8 ± 27.3 versus 5.9 ± 21.5 mm Hg in the placebo group). Response to treatment was categorized as improvement (assigned a value of 2), no progression (assigned a value of 1), and progression (assigned a value of 0). Response was significantly better in the EN group (1.4 ± 0.8) compared with the placebo group (0.3 ± 0.5). These results suggest that EN treatment is beneficial in dogs with naturally occurring idiopathic GN.

Key words: Angiotensin-converting enzyme inhibition; Kidney; Renal.

Canine glomerulonephritis (GN) is both a common renal disease and a leading cause of chronic renal insufficiency and failure.1 Glomerulonephritis usually results from the presence of immune complexes in the glomerular capillary walls.2 Immune complexes accumulate in the glomerulus secondary to either deposition of preformed circulating complexes or by in situ immune complex formation. Subsequently, glomerular cell proliferation, thickening of the glomerular capillary walls, and eventually glomerular hyalinization and sclerosis occur. Loss of plasma proteins into the urine is one of the earliest functional defects recognized in GN. Consequences of proteinuria may include sodium retention, edema, ascites, hypercholesterolemia, hypertension, hypercoagulability, muscle wasting, and weight loss. Although it has not been documented in the dog, proteinuria in human beings promotes protein accumulation within the glomerular tuft, which stimulates mesangial cell proliferation and increased mesangial matrix production.3 In addition, excessive amounts of protein in the glomerular filtrate can be toxic to human tubular epithelial cells and can lead to interstitial inflammation, fibrosis, and tubular cell death.4 Chronic interstitial nephritis frequently is the histopathologic lesion observed in dogs with chronic renal failure, but this end-stage lesion can result from primary glomerular or tubular lesions. Once any portion of the nephron is irreversibly damaged, the entire nephron becomes nonfunctional and is replaced by fibrous tissue.

Treatment of GN has received substantially less attention in veterinary medicine than has the treatment of chronic renal failure. Inasmuch as immune complexes usually initiate GN, elimination of the source of antigenic stimulation is the primary goal of treatment. Unfortunately, elimination of the antigen source often is not possible because the antigen source may not be identified or the underlying disease basis of the disease. On the basis of clinical trials in human beings, corticosteroids, azathioprine, chlorambucil, cyclophosphamide, and cyclosporine have been used in dogs with GN to decrease immunoglobulin production. Despite the widespread use of immunosuppressive agents, only cyclosporin has been subjected to a controlled clinical trial. In a previous study, cyclosporin treatment did not reduce proteinuria associated with idiopathic GN in dogs.5 A growing body of evidence indicates that angiotensin-converting enzyme inhibitors (ACEIs) reduce systemic blood pressure and urinary protein excretion and slow the progression of renal disease in human beings and dogs. Benazepril administration slowed the rate of disease progression in a multicenter, 3-year clinical trial involving 583
human beings with various renal disorders.\textsuperscript{7} The best re-
response was observed in patients with glomerular disease and proteinuria greater than 1.0 g per 24 hours.\textsuperscript{2} In another clinical trial involving human beings with non-diabetic pro-
gressive renal insufficiency, enalapril (EN) administration decreased proteinuria and hypertension and slowed the de-
cline in glomerular filtration rate observed in patients treat-
ed with a placebo.\textsuperscript{4} In a 2-year double-blind prospective
study involving 29 non-diabetic proteinuric human patients,
the short-term antiproteinuric effects of EN correlated in-
versely with the slope of renal functional decline.\textsuperscript{8} This
observation was confirmed in another long-term study of
proteinuric, non-diabetic renal disease in people.\textsuperscript{10}

In experimental dogs subjected to unilateral nephrectomy
and diabetes mellitus, lisinopril administration was shown
to reduce glomerular transcapillary hydraulic pressure and
glomerular cell hypertrophy as well as proteinuria.\textsuperscript{11} EN
treatment of Samoyed dogs with X-linked hereditary nep-
hratitis decreased proteinuria, improved renal excretory
function, decreased glomerular basement membrane mem-
branch splitting, and prolonged survival compared with control dogs.\textsuperscript{12}

On the basis of these promising results, the present study
was undertaken to assess the effects of EN on naturally
occurring idiopathic canine GN.

Materials and Methods

Patient Selection and Management

Dogs with proteinuria (urine protein/creatinine ratio (UP/C) > 3.0
with normal urine sediments or those containing hyaline casts) and
biopsy-proven GN were accepted for study from the patient popula-
tions of 6 veterinary teaching hospitals. Dogs were excluded from the
study if they had a concurrent disease that is associated with a high
prevalence of GN, the treatment of which could result in attenuation
of the proteinuria (eg, dirofilariais, ehrlichiosis, systemic lupus ery-
thematosus, or neoplasia); if they had persistent serum creatinine
(SrCr) > 3.0 mg/dL; or if they had biopsy evidence of glomerular
amyloidosis or moderate to severe sclerosis or hyalinization of the
glomerular tufts.

Before treatment, the following were obtained for each dog: com-
plete physical examination, CBC with platelet count, serum biochem-
sity profile, urinalysis, UP/C, antinuclear antibody, Dirofilaria immitis
and Ehrlichia canis serology, thoracic and abdominal radiographs,
blood clotting analysis, and renal biopsy with routine histopathologic
examination. Indirect systolic blood pressure (SBP; Doppler or oscil-
lometric technique) was measured. SBP values were the average of at
least 6 determinations. The cuff size, extremity, and body position
were consistent at each determination. Initial evaluations also may
have included additional tests as deemed appropriate for each case (eg,
adenocorticotrophic hormone stimulation test, Borrelia burgdorferi se-
rology). For dogs in which a concurrent urinary tract infection was
diagnosed, appropriate antibiotic treatment followed by documenta-
tion of a normal urine sediment (with the exception of hyaline casts) and
negative urine culture were obtained before determining the UP/C.
Although clinical methodologies for the previously mentioned tests
varied among institutions, all methods were used routinely in the re-
spective clinical settings.

Dogs meeting the above entry criteria were randomized into 1 of 2
groups after written consent was received from the owners. Random-
ization was stratified according to the initial morphologic diagnosis.
Groups were designated to receive either EN\textsuperscript{\textsuperscript{a}} or placebo for 6 months.
The placebo tablets contained the EN vehicle only. These tablets were
identical to the various-sized EN tablets and were provided by Merck
& Co Inc. The attending clinicians and pet owners had no knowledge
of the treatment status. The initial dosage of EN/placebo was 0.5 mg/
kg PO q24h. This dosage was increased to 0.5 mg/kg q12h after 30
days of treatment if the UP/C remained at >50% of the baseline value.

In addition to the EN/placebo regiment, all dogs were treated with
low-dose aspirin (0.5–5 mg/kg PO q12–24h) and fed a commercial
diet of reduced protein, phosphorus, and sodium.\textsuperscript{2} Follow-up exa-
ninations were performed at 1, 3, and 6 months and included the fol-
lowing: physical examination, CBC with platelet count, serum bio-
chemistry profile, urinalysis with UP/C, and SBP. At the end of the
study, response to treatment was scored as improvement (>50% re-
duction in UP/C with stable SrCr; assigned a value of 2), no progress-
ion (<50% reduction in UP/C with stable SrCr; assigned a value of
1), and progression (>50% increase in UP/C, SrCr, or both, or renal
failure, leading to euthanasia; assigned a value of 0). In another sepa-
rate analysis of response to treatment, an increase in SrCr > 0.2 mg/
dl over the course of the study was considered an indication of disease
progression.

Morphologic Diagnoses

Renal tissue from each dog was sectioned at 3–5 μm and stained
with hematoxylin and eosin and periodic acid–Schiff. To aid in ran-
domization of dogs into treatment groups, the initial morphological
diagnoses were made by the attending pathologist at the institution
where the dog was treated. A single pathologist (DMG) subsequently
evaluated all slides in order to obtain a consistent morphological di-
agnosis. During this second evaluation, the morphological diagnosis
was classified as membranous GN if there was diffuse capillary wall
thickening without an appreciable increase in glomerular cellularity,
or membranoproliferative GN if both glomerular cell hyperplasia and
capillary wall thickening were observed. The glomerular changes ad-
ditionally were graded as minimal, mild, moderate, and marked.

Data Analyses

Student’s t-test was used to determine differences between mean
clinicopathologic results for the placebo and EN-treated groups before
and after 6 months of treatment. Of the parameters analyzed, only UP/
C was significantly different at baseline and therefore each individual
dog’s UP/C was calculated as a change from baseline (ΔUP/C). Linear
regression analysis was used to determine if a correlation existed be-
tween ΔUP/C and ΔSBP for the 2 groups. Data also were analyzed
before and after 1, 3, and 6 months for each group with a repeated-
measures analysis of variance procedure. A chi-square goodness-of-fit
test was used to evaluate the categorical data (renal histology and
response to therapy). Finally, the ability of EN treatment to prevent
increases in SrCr ≥ 0.2 mg/dL over the course of the study was cal-
sulated as the attributable risk reduction. Values were considered sig-
nificantly different at P < .05. All statistical analyses were performed
with commercial software packages\textsuperscript{\textsuperscript{\textsuperscript{a}}} on a personal computer.

Results

Dogs with GN were evaluated at participating institutions
between January 1995 and October 1998. Twenty-nine
dogs entered the study from 6 institutions (Colorado State
University, n = 13; University of California-Davis, n = 7;
North Carolina State University, n = 5; Ohio State Uni-
versity, n = 2; University of Georgia, n = 1; and University of
Minnesota, n = 1).

Fourteen dogs were randomly assigned to the placebo
treatment group and 15 dogs were randomly assigned to the
EN treatment group (1 dog from North Carolina State Uni-
versity was first treated with the placebo for 6 months and
then with EN for an additional 6 months). Table 1 provides
the following information for dogs in the 2 treatment

Table 1. Values for dogs treated with placebo and enalapril at baseline and at 6 months after treatment.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo Treatment Group (mean ± SD)</th>
<th>Enalapril Treatment Group (mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>7.5 ± 3.4</td>
<td>7.3 ± 2.3</td>
</tr>
<tr>
<td>Histologic grade</td>
<td>2.4 ± 0.8</td>
<td>2.4 ± 0.7</td>
</tr>
<tr>
<td>SrCr (mg/dL)</td>
<td>1.6 ± 0.6</td>
<td>1.9 ± 0.6</td>
</tr>
<tr>
<td>Serum albumin (g/dL)</td>
<td>2.4 ± 0.8</td>
<td>2.2 ± 0.5</td>
</tr>
<tr>
<td>UP/C ratio</td>
<td>4.7 ± 2.3</td>
<td>8.7 ± 4.4</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>148 ± 25</td>
<td>154 ± 25</td>
</tr>
<tr>
<td>SrCr × UP/C ratio</td>
<td>7.5 ± 4.5</td>
<td>15.3 ± 7.2</td>
</tr>
<tr>
<td>At 6-month follow-up</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SrCr (mg/dL)</td>
<td>2.7 ± 1.5</td>
<td>1.7 ± 0.7</td>
</tr>
<tr>
<td>Serum albumin (g/dL)</td>
<td>2.1 ± 0.9</td>
<td>2.3 ± 0.6</td>
</tr>
<tr>
<td>UP/C ratio</td>
<td>6.6 ± 4.5</td>
<td>3.7 ± 3.8</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>155.5 ± 14</td>
<td>142 ± 19</td>
</tr>
<tr>
<td>SrCr × UP/C ratio</td>
<td>16 ± 11</td>
<td>7.6 ± 9.4</td>
</tr>
<tr>
<td>Response*</td>
<td>0.3 ± 0.5</td>
<td>1.4 ± 0.8</td>
</tr>
</tbody>
</table>

SD, standard deviation; SrCr, serum creatinine; UP/C, urine protein/creatinine.

* Response was coded as follows: 2 = improvement (≥50% reduction in UP/C ratio with stable SrCr); 1 = no progression (<50% reduction in UP/C ratio with stable SrCr); and 0 = progression (>50% increase in UP/C ratio, SrCr, or both, or euthanasia administered as a result of the dog’s renal failure).

At baseline, there was no difference in CBC or serum biochemistry profile parameters, SBP, or glomerular histologic grade between groups, but UP/C was significantly greater in the EN treatment group compared with the placebo treatment group (8.7 ± 4.4 versus 4.7 ± 2.3). In the EN treatment group, 8 dogs had membranous GN and 8 dogs had membroproliferative GN. In the placebo group, 8 dogs had membranous GN and 6 dogs had membroproliferative GN. EN was administered to 14 dogs for 6 months, to 1 dog for 5 months, and to 1 dog for 3 months. Two of the dogs in the EN treatment group were euthanized because of renal failure, one at 3 months and the other at 5 months. EN was administered once daily throughout the study to 7 dogs, whereas twice-daily administration was initiated for 6 dogs at 1 month and for the remaining 3 dogs at 3 months. The placebo was administered to all 14 dogs for 6 months. Once-daily administration of the placebo was maintained in 3 dogs, whereas twice-daily administration was initiated for 9 dogs at 1 month and for the remaining 2 dogs at 3 months.

There were no significant differences documented by repeated-measures analysis of variance in any of the clinicopathologic parameters within groups or between groups at 1 and 3 months, but a significant interaction between treatments and the repeated measurements (time) was observed, resulting in an inflation of the error mean square. Therefore, the change in parameters between baseline and 6 months was analyzed with Student’s t-test for differences between treatment groups. After 6 months of treatment, the ΔUP/C from baseline was significantly different between groups (Fig 1; Table 2). When data were adjusted for changes in SrCr (SrCr × UP/C) a similar significant reduction was noted (Fig 2; Table 2). The change in SBP after 6 months of treatment also was significantly different between groups when evaluated by Student’s t-test (Fig 3; Table 2). Although not statistically significant, the increase in SrCr over the course of the study was greater in the placebo group compared with the EN group (Table 2). Increases in SrCr ≥ 0.2 mg/dL at 6 months were observed in 13 of 14 placebo group dogs and in 3 of 16 dogs in the EN group. The attributable risk reduction calculation indicated a 91.2% chance (95% confidence interval, 77.5–

![Delta Urine Protein/Creatinine Ratio](image)

Fig 1. Change in the urine protein/creatinine ratio (ΔUP/C) for the EN and placebo treatment groups at 1, 3, and 6 months.
Table 2. Comparison of the changes ($\Delta$) in urine protein/creatinine (UP/C) ratio, systolic blood pressure (SBP), serum creatinine (SrCr), and SrCr $\times$ UP/C between enalapril and placebo-treated dogs 6 months after treatment.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Enalapril Treatment Group (mean ± SD)</th>
<th>Placebo Treatment Group (mean ± SD)</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\Delta$UP/C</td>
<td>$-4.2 ± 1.4$</td>
<td>$1.9 ± 0.9$</td>
<td>.001</td>
</tr>
<tr>
<td>$\Delta$SBP (mm Hg)</td>
<td>$-12.8 ± 27.3$</td>
<td>$5.9 ± 21.5$</td>
<td>.045</td>
</tr>
<tr>
<td>$\Delta$SrCr (mg/dL)</td>
<td>$0.33 ± 1.68$</td>
<td>$1.12 ± 1.28$</td>
<td>.16</td>
</tr>
<tr>
<td>$\Delta$SrCr $\times$ UP/C</td>
<td>$-2.2 ± 15.2$</td>
<td>$8.4 ± 10.1$</td>
<td>.03</td>
</tr>
</tbody>
</table>

SD, standard deviation.

100%) that EN treatment prevented an increase in SrCr to $\geq 0.2$ mg/dL. No differences in serum albumin or cholesterol concentrations were noted between the 2 groups at any time in the study, and no correlation was established by linear regression analysis between the $\Delta$UP/C and $\Delta$SBP in either group. The serum cholesterol concentrations for the EN group at baseline and 6 months were $355 ± 140$ and $376 ± 117$ mg/dL, respectively. Serum cholesterol concentrations for the placebo group at baseline and 6 months were $397 ± 66$ and $391 ± 77$ mg/dL, respectively. No dog developed persistent nephrotic syndrome.

In the EN treatment group, 9 dogs improved, 4 dogs had no progression, and 3 dogs had progression of their renal disease (Fig 4). One dog in the EN group was euthanized because of renal failure after 3 months of treatment and another was euthanized after 5 months of treatment. The clinicopathologic parameters obtained from these 2 dogs before euthanasia were used as the end point for 6-month data. Of 9 EN-treated dogs with improved renal function, 2 dogs showed continued decreases in UP/C and SrCr $\times$ UP/C throughout the 6 months of treatment. The remaining 7 dogs showed marked decreases in UP/C and SrCr $\times$ UP/C within the first month of treatment, with only slight continued decreases in these parameters at 3 and 6 months. Within the placebo treatment group, 0 dogs improved, 4 dogs had no progression, and 10 dogs had progression of their renal disease. The dog first treated with the placebo for 6 months and then with EN for 6 months had no progression during the placebo treatment and then had improved renal function during the EN treatment. Statistical evaluation of the categorical response to treatment showed that the EN-treated dogs (1.4 ± 0.8) did significantly better compared with the placebo-treated dogs (0.3 ± 0.5) (Fig 4; Table 1). Retrospectively, no differences in the initial clinicopathologic or histologic parameters were observed in either group between those dogs that improved, had no progression, or had disease progression.

### Discussion

The results of this study suggest that EN treatment can reduce proteinuria and delay the onset or progression of azotemia in dogs with idiopathic, naturally occurring GN. These results compare favorably to another study of naturally occurring canine renal disease where EN treatment slowed the increase in proteinuria and SrCr concentrations and prolonged survival in Samoyed dogs with X-linked hereditary nephritis. In contrast to this previous study, EN treatment significantly reduced SBP in dogs with GN in the present study. In another study of uninephrectomized Beagles with alloxan-induced diabetes mellitus, treatment with lisinopril decreased proteinuria, glomerular capillary pressure and hypertrophy, and mean arterial pressure. Attenuation of proteinuria was more consistent than attenuation of systemic blood pressure in these studies, suggesting that ACEIs may have more effect on intraglomerular pressure than systemic pressure. Similar to the results of the present study, several clinical trials of in human beings with non-diabetic, proteinuric renal disease have shown that ACEIs...
change systemic blood pressure and proteinuria. All of these studies suggest that angiotensin II has a role in the pathophysiology of proteinuric renal disease.

Angiotensin II is generated from the conversion of angiotensin I by converting enzyme, which is found in abundance on vascular endothelial cells and on the brush border of proximal tubular epithelial cells. Angiotensin II can be generated in the systemic circulation and delivered to the kidney, or it can be generated within the kidney by local conversion of angiotensin I. Angiotensin II receptors are concentrated within the kidney and are present in glomeruli and the renal tubular vasculature. Angiotensin II has multiple actions within the kidney that can contribute to the pathophysiology of renal disease. For example, angiotensin II causes vasoconstriction of glomerular arterioles, the efferent to a greater extent than the afferent, which results in increased intraglomerular capillary pressure. Angiotensin II also increases glomerular transport of macromolecules such as protein by 2 mechanisms: increased convective transport mediated by increased intraglomerular capillary pressure and increased mesangial uptake. Finally, angiotensin II acts as a growth factor for vascular and tubular structures in the kidney and increases the production of other growth factors and vasoactive substances such as transforming growth factor beta 1, thromboxane, and endothelin-1 in rats. Although angiotensin II concentrations
and converting enzyme activity were not measured in the present study, previous work in dogs has shown that 0.5 mg/kg of EN administered once daily decreases angiotensin-converting enzyme activity for more than 24 hours.20

Treatment with ACEIs probably decreases proteinuria and preserves renal function associated with glomerular disease by several mechanisms. In dogs, administration of lisinopril decreases efferent glomerular arteriolar resistance, which results in decreased glomerular transcapillary hydraulic pressure and decreased proteinuria.21 In rats, administration of EN prevents the loss of glomerular heparan sulfate that can occur with glomerular disease.21,22 Administration of ACEIs also is thought to attenuate proteinuria by decreasing the size of glomerular capillary endothelial cell pores in people.23,24 In addition, the antiproteinuric and renal protective effects of ACEIs may be associated with improved lipoprotein metabolism. Lipid deposition in the glomerular mesangium can contribute to proteinuria and glomerulosclerosis. In human beings with nephrotic range proteinuria, administration of ACEI not only decreases proteinuria but also reduces plasma concentrations of low-density lipoprotein cholesterol and triglycerides.25 In the present study, however, EN treatment did not decrease serum cholesterol concentrations compared with placebo-treated dogs. Administration of lisinopril in dogs can also slow glomerular mesangial cell growth and proliferation that can alter the permeability of the glomerular capillary wall and lead to glomerulosclerosis.11 Finally, ACEIs are nonspecific enzyme inhibitors, and in addition to blocking the conversion of angiotensin I to angiotensin II, they also inhibit the degradation of bradykinin by blocking kininase II. Bradykinin is a vasodilatory hormone that selectively dilates efferent glomerular arterioles and enhances the formation of nitric oxide and prostacyclin. Accumulation of bradykinin is thought to have beneficial renal effects in rats and dogs.26,27

The additional treatments used in this study were designed to decrease platelet aggregation (low-dose aspirin) and the hypercoagulation associated with proteinuria and to reduce dietary protein, phosphorus, and sodium (Prescription Diet Canine k/d®). The low-dose aspirin treatment may have had a beneficial effect in both groups by decreasing thromboxane production. Although the beneficial effects of lowered dietary protein on renal disease progression remains controversial, high dietary protein may promote proteinuria in dogs.28 We believe that low-dose aspirin and moderately reduced dietary protein, phosphorus, and sodium represent standard care for dogs with GN. In addition, previous studies in human beings have shown that reduced dietary protein and ACEIs tend to have an additive effect on glomerular capillary pressure.29,30 Decreased dietary protein decreases preglomerular resistance and ACEIs exert most of their vasodilatory effect on postglomerular resistance.

Nine of 16 dogs treated with EN in this study had improved renal function: 4 had no improvement (stable renal function) and 3 had progression of their renal disease. Similar variable responses to treatment with ACEIs have been observed in studies of rats with glomerulosclerosis29,32 and adriamycin nephrosis.33 The decreased response to ACEIs in some individuals could be associated with more severe initial renal disease (eg, glomerulosclerosis), although in the current study, the nonresponding dogs had similar initial renal morphologic and functional changes compared with dogs that did respond to EN treatment. Variable response to treatment in this study also could be associated with differences in the underlying cause of the GN. Two of the EN-treated dogs had severe declines in renal function that resulted in euthanasia at 3 and 5 months into the study. Administration of ACEIs can cause renal excretory function to decrease. This functional decline in people usually is acute and reversible with discontinuation of the ACEI.34 The functional declines in the 2 dogs in this study that were euthanized were gradual and unresponsive to discontinued EN treatment. In some human beings, deterioration in renal function associated with ACEI is not reversible.35 It is possible that EN treatment could have had a role in the renal excretory functional decline in the 3 dogs that had progression of disease (increases in SrCr) in this study. In the 4 dogs that had stable renal function (no progression or improvement) in the face of EN treatment, it is possible that treatment of longer duration may have resulted in improved renal function. In a recent study of human beings with chronic, proteinuric nephropathies, ≥36 months of continued ramipril treatment was required to increase glomerular filtration rate and decrease the risk of end-stage renal failure.35

The criteria used to define a positive response to treatment in this study were a ≥50% reduction in proteinuria and a stable or decreasing SrCr. Studies in human beings36 and rats37 show that proteinuria is a risk factor for the progression of renal disease. Further, urinary protein excretion rate was found to be the best independent predictor of end-stage renal failure in a study of people with nondiabetic, proteinuric chronic nephropathy.38 In this previous study, the higher the urinary protein excretion, the faster the subsequent decline in glomerular filtration rate and, even more important, the faster the progression to end-stage renal failure.37

This present study has several important limitations. Glomerular filtration rate was not measured, follow-up renal biopsies were not obtained, and the duration of treatment was relatively short. The use of dogs with naturally occurring disease undoubtedly resulted in variation of disease as well as variation in the progression of disease. Multicenter clinical trials also have inherent differences in clinician approach to patients and diagnostic methodology. Given these limitations, it is still clear that the EN group had better response to treatment than did the placebo group. These results suggest that EN treatment of idiopathic GN of dogs is associated with decreased proteinuria and delayed progression of azotemia; however, it is important to note that not all EN-treated dogs in this study responded and that all of the deaths occurred in the dogs in the EN treatment group. Further studies are needed to evaluate longer term treatment in larger groups of dogs with both experimentally induced and naturally occurring GN. Studies also are needed to try and determine which dogs with GN will and which will not respond to ACEI treatment. Finally, similar studies should also be performed in dogs with early generalized end-stage renal failure. Until the results of further studies...
in dogs are available, EN should be used cautiously in dogs with GN.

Footnotes

* Merck Ag Vet Division, Merck & Co Inc, Rahway, NJ
† Prescription Diet Canine k/d, Hill’s Pet Nutrition, Topeka, KS
‡ Microsoft Excel 97, Seattle, WA
§ PC-SAS, Statistical Analysis Systems, Raleigh, NC

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