Treatment of glomerular diseases: pioneering clinical trials

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KEYWORDS: amyloidosis; calcineurin inhibitors; corticosteroids; Fabry disease; focal segmental glomerulosclerosis; glomerulonephritis; glomerulus; membranous nephropathy; nephrotic syndrome; stem cell transplant

This year will be the 60th anniversary of the International Society of Nephrology's flagship journal, *Kidney International* (*KI*). *KI* has published articles that have advanced clinical nephrology since its inception. The selection of articles included below has led to significant changes in patient management in the editor's opinion.

Shorter term corticosteroids are equally effective as longer term in primary nephrotic syndrome in children

Yoshikawa N, Nakanishi K, Sako M, et al., for the Japanese Study Group of Kidney Disease in Children. A multicenter randomized trial indicates initial prednisolone treatment for childhood nephrotic syndrome for two months is not inferior to six-month treatment. **Kidney Int.** ***2015;87:225–232.***

Sinha A, Saha A, Kumar M, et al. Extending initial prednisolone treatment in a randomized control trial from 3 to 6 months did not significantly influence the course of illness in children with steroid-sensitive nephrotic syndrome. **Kidney Int.** ***2015;87:217–224.***

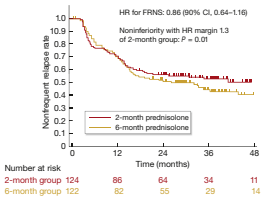

Figure 1 |

The vast majority of children with primary nephrotic syndrome are steroid sensitive and do not progress to end-stage kidney disease (ESKD). However, relapses are seen in up to 90% of children with 50% of them experiencing frequent relapses. The majority of children who respond to corticosteroids do so within 4 weeks. Traditionally, the total treatment duration with corticosteroids was up to 5 months as discussed in the 2012 KDIGO guideline.[1] However, it was not clear whether shorter exposure to corticosteroids would be equally effective in preventing relapse and reducing adverse effects of corticosteroids.

In the last few years, 2 randomized controlled trials (RCTs)[2,3] reported in *KI* have evaluated shorter duration corticosteroid dosage (2–3 months vs. 6 months) for the treatment of the initial episode of steroid-sensitive nephrotic syndrome in children. These studies show that extending initial corticosteroid treatment from 8 to 12 weeks to 6 months may delay the first relapse but does not have an impact on the occurrence of frequent relapses, nor on the subsequent disease course. However, although these studies do not suggest that the shorter course in itself has a better safety profile, it is possible that in the long term, shorter periods of corticosteroid treatment for relapses may limit cumulative steroid toxicity. A more recent trial from the United Kingdom (PREDNOS) showed similar times to relapse and relapse rates with short-term (8 weeks) versus 16 weeks of corticosteroids. In the latter study, there was a positive effect on short-term health economic benefit through reduced resource use and increased quality of life.[4]

Figure 1 is adapted with permission from Yoshikawa N, Nakanishi K, Sako M, et al., for the Japanese Study Group of Kidney Disease in Children. A multicenter randomized trial indicates initial prednisolone treatment for childhood nephrotic syndrome for two months is not inferior to six-month treatment. *Kidney Int.* 2015;87:225–232.[2] Copyright © 2015 International Society of Nephrology.

Editor's Note

This article is part of the *KI* International Society of Nephrology 60th anniversary series. This month's topic is the treatment of glomerular disease.

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Calcineurin inhibitors in focal segmental glomerulosclerosis and membranous nephropathy

Cattran DC, Appel GB, Hebert LA, et al., for the North America Nephrotic Syndrome Study Group. A randomized trial of cyclosporine in patients with steroid-resistant focal segmental glomerulosclerosis. **Kidney Int.** ***1999;56:2220–2226.***

Cattran DC, Appel GB, Hebert LA, et al., for the North American Nephrotic Syndrome Study Group. Cyclosporine in patients with steroid-resistant membranous nephropathy: a randomized trial. **Kidney Int.** ***2001;59:1484–1490.*** Persistent, nephrotic-range proteinuria is an important risk factor for renal progression in primary glomerular disease. The introduction of calcineurin inhibitors (CNIs) revolutionized the outcome of solid organ transplants, and interest grew in using these drugs to induce remission of proteinuria in glomerular diseases. After the publication of several case reports and nonrandomized trials, 2 randomized controlled trials were reported by the North American Nephrotic Syndrome Study Group on the use of cyclosporine in focal segmental glomerulosclerosis (FSGS) and membranous nephropathy.[5,6]

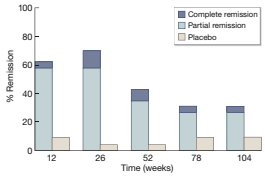

Figure 2|

In the trial of cyclosporine in patients with steroid-resistant FSGS, 49 patients were treated with 26 weeks of cyclosporine with low-dose prednisone versus placebo and were followed for an average of 200 weeks.[5] Cyclosporine doses were titrated to achieve trough levels of 125 and 225 μg/l. Prednisone dose was 0.15 mg/kg per day to a maximum of 15 mg. A total of 70% of patients in the treated group versus 4% in the placebo group achieved remission (partial or complete) by 25 weeks. However, relapse was seen in 40% of patients who remitted by 1 year and 60% by 1.5 years. Interestingly, renal function was better preserved in the cyclosporine-treated group.

In patients with steroid-resistant membranous nephropathy, cyclosporine and low-dose prednisone were administered in a similar regimen as in the FSGS study for 26 weeks and patients were followed for an average of 1.5 years.[6] The rate of complete or partial remission was higher in the cyclosporine/prednisone group versus placebo (75% vs. 22%) by week 26, and 43% of treated patients versus 40% in the placebo group experienced a relapse by week 52. There was no change in renal function in the 2 groups.

CNIs are now commonly used in both FSGS and membranous nephropathy. CNIs may be used as initial treatment in patients with FSGS who have a relative contraindication to corticosteroids and as second-line therapy in corticosteroid-resistant patients.[1] In membranous nephropathy, although CNIs may be employed as an alternative to first-line therapy to cyclophosphamide/steroid regimens, or as second-line treatment for patients who have failed cyclophosphamide,[1] a recent randomized controlled trial (MENTOR) reported on superior outcomes with rituximab compared with cyclosporine in patients with membranous nephropathy.[7] Relapse rates appear to be fairly high with short duration of CNI therapy in both conditions. Prolonged use of CNIs may potentially be associated with nephrotoxicity.

Figure 2 is adapted with permission from Cattran DC, Appel GB, Hebert LA et al., for the North American Nephrotic Syndrome Study Group. A randomized trial of cyclosporine in patients with steroid-resistant focal segmental glomerulosclerosis. *Kidney Int.* 1999;56:2220–2226.[5]

High-dose melphalan and autologous stem cell transplantation is feasible in end-stage kidney failure patients with amyloid light-chain (AL) amyloidosis

Casserly LF, Fadia A, Sanchorawala V, et al. High-dose intravenous melphalan with autologous stem cell transplantation in AL amyloidosis-associated end-stage renal disease. **Kidney Int.** ***2003;63:1051–1057.*** The prognosis of AL amyloidosis before the early 1990s was dismal, especially in patients with ESKD or heart failure. The standard treatment for AL amyloid with cyclic oral melphalan and corticosteroids was associated with median survival rates of only 16 to 18 months and rare eradication of the plasma cell dyscrasia.[8] Studies demonstrating favorable response rates to high-dose melphalan with autologous stem cell transplant for AL amyloidosis began to appear in the

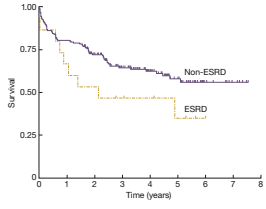

Figure 3|

mid-1990s.[9] Many patients with ESKD were excluded from such studies.

The small pilot study reported in *KI* compared the outcomes after high-dose melphalan and autologous stem cell transplantation in 15 patients with ESKD compared with 180 patients without ESKD, which is notable for several key findings.

(i) Complete hematological remission occurred in 8 of the 15 patients (53%) 12 months after treatment.

(ii) Survival in the patients with hematological remission was impressive with 6 of the 8 patients (75%) alive at a median follow-up of 4.5 years (vs. 13–26 months in those patients who did not go into hematological remission).[10] Survival was similar in the ESKD versus non-ESKD group. The median survival of 25 months in this study exceeded previous reports for traditional regimens.

(iii) There were 2 deaths (13%) within 30 days of stem cell infusion (one from ventricular arrhythmia, one from respiratory failure). Expected toxicities including mucositis and cytopenias were more common in patients with ESKD versus patients without ESKD, but otherwise the 2 groups were similar in this respect.

(iv) Finally, and importantly, 3 patients were able to receive a renal transplant after achieving hematological remission with functioning allografts, 5–6 years after transplantation.

In sum, this pilot study showed that high-dose i.v. melphalan followed by autologous stem cell transplantation though associated with significant toxicity could prolong survival in patients with ESKD, some of whom were then able to receive a renal transplantation after achieving hematological remission. This study was the harbinger of many subsequent reports, and it is now routine in many centers around the world to treat AL amyloidosis patients with ESKD with high-dose melphalan and autologous stem cell transplantation. This approach along with major advances in plasma cell–directed therapy such as proteasome inhibitors, thalidomide derivatives, and anti–CD-38 antibodies has changed the lives of many patients with this previously terminal disease.

Figure 3 is adapted with permission from Casserly LF, Fadia A, Sanchorawala V, et al. High-dose intravenous melphalan with autologous stem cell transplantation in AL amyloidosis- associated end-stage renal disease. *Kidney Int.* 2003;63:1051–1057.[10] Copyright © 2003 International Society of Nephrology.

Renal effects of enzyme replacement therapy in Fabry disease (FD)

Thurberg BL, Rennke H, Colvin RB, et al. Globotriaosylceramide accumulation in the Fabry kidney is cleared from multiple cell types after enzyme replacement therapy. **Kidney Int. *2002;62:1933–1946.*** FD is an X-linked recessive disease resulting from the deficiency of the lysosomal enzyme α-galactoside A leading to accumulation of neutral glycosphingolipids, mainly globotriaosylceramide. Recombinant human α-galactosidase A replacement therapy became available in the early 2000s and was associated with amelioration of some of the clinical manifestations of FD. The effects on renal pathology were outlined in a sub-study of the 5-month phase 3 randomized controlled trial of 58 patients with FD treated with recombinant human α-galactosidase A.[11] A total of 48 patients had biopsies at baseline, 5 months, and 11 months. At baseline, globotriaosylceramide accumulation was noted in vascular endothelial and smooth muscle cells, mesangial cells, and interstitial cells. Particularly, dense accumulation was seen in podocytes and distal tubular cells. After 11 months of recombinant human α-galactosidase A, there was almost complete clearance of globotriaosylceramide from vascular endothelial cells, mesangial cells, and cortical interstitial cells.[12] Podocytes and distal tubular cells showed less clearance. This study clearly showed the ameliorative effects on renal histology of enzyme replacement therapy in FD.

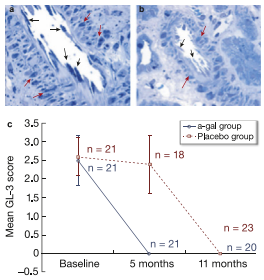

Figure 4|

Figure 4 is adapted with permission from Thurberg BL, Rennke H, Colvin RB, et al. Globotriaosylceramide accumulation in the Fabry kidney is cleared from multiple cell types after enzyme replacement therapy. *Kidney Int.* 2002;62:1933–46.[12] Copyright © 2002 International Society of Nephrology.

DISCLOSURE

The author declared no competing interests.

REFERENCES

1. Kidney Disease: Improving Global Outcomes (KDIGO) Glomerulonephritis Work Group. KDIGO Clinical Practice Guideline for Glomerulonephritis. *Kidney Int Suppl.* 2012;2:139–274.

2. Yoshikawa N, Nakanishi K, Sako M, et al, for the Japanese Study Group of Kidney Disease in Children. A multicenter randomized trial indicates initial prednisolone treatment for childhood nephrotic syndrome for two months is not inferior to six-month treatment. *Kidney Int*. 2015;87:225–232.
3. Sinha A, Saha A, Kumar M, et al. Extending initial prednisolone treatment in a randomized control trial from 3 to 6 months did not significantly influence the course of illness in children with steroid-sensitive nephrotic syndrome. *Kidney Int*. 2015;87:217–224.
4. Webb NJA, Woolley RL, Lambe T, et al. Long term tapering versus standard prednisolone treatment for first episode of childhood nephrotic syndrome: phase III randomised controlled trial and economic evaluation. *BMJ*. 2019;365:l1800.
5. Cattran DC, Appel GB, Hebert LA, et al, for the North America Nephrotic Syndrome Study Group. A randomized trial of cyclosporine in patients with steroid-resistant focal segmental glomerulosclerosis. *Kidney Int*. 1999;56:2220–2226.
6. Cattran DC, Appel GB, Hebert LA, et al, for the North American Nephrotic Syndrome Study Group. Cyclosporine in patients with steroid-resistant membranous nephropathy: a randomized trial. *Kidney Int*. 2001;59:1484–1490.
7. Fervenza FC, Appel GB, Barbour SJ, et al. Rituximab or cyclosporine in the treatment of membranous nephropathy. *N Engl J Med*. 2019;381:36–46.
8. Kyle RA, Gertz MA, Greipp PR, et al. A trial of three regimens for primary amyloidosis: colchicine alone, melphalan and prednisone, and melphalan, prednisone, and colchicine. *N Engl J Med*. 1997;336:1202–1207.
9. Comenzo RL, Vosburgh E, Falk RH, et al. Dose-intensive melphalan with blood stem-cell support for the treatment of AL (amyloid light-chain) amyloidosis: survival and responses in 25 patients. *Blood*. 1998;91:3662–3670.
10. Casserly LF, Fadia A, Sanchorawala V, et al. High-dose intravenous melphalan with autologous stem cell transplantation in AL amyloidosis-associated end-stage renal disease. *Kidney Int*. 2003;63:1051–1057.
11. Eng CM, Guffon N, Wilcox WR, et al. Safety and efficacy of recombinant human alpha-galactosidase A—replacement therapy in Fabry's disease. *N Engl J Med*. 2001;345:9–16.
12. Thurberg BL, Rennke H, Colvin RB, et al. Globotriaosylceramide accumulation in the Fabry kidney is cleared from multiple cell types after enzyme replacement therapy. *Kidney Int*. 2002;62:1933–1946.