Supportive Therapy Can Be as Good as Immunosuppression in IgA Nephropathy

By Daniel M. Keller

Optimal supportive therapy (SUP) can obviate the need for immunosuppression in treating progressive IgA nephropathy (IgAN), a new study shows. Among patients with biopsy-proven IgAN, SUP drove 30 percent of them into a low-risk category, slowing their loss of renal function and overcoming the benefits of immunosuppression.

For the prospective Supportive Versus Immunosuppressive Therapy for Progressive IgA Nephropathy (STOP-IgAN) trial, eligible adult patients at 32 nephrology centers underwent a 6-month run-in phase of SUP using antihypertensive, antiproteinuric (ACE inhibitor or angiotensin-receptor blocker), and statin medications as well as dietary counseling. Patients with persistent proteinuria >0.75 g/day at the end of the run-in were randomly assigned in an open-label manner to SUP or to SUP plus immunosuppressive therapy for 3 years. At the 52nd annual meeting of the European Renal Association—European Dialysis and Transplant Association conference in London in May 2015, Jürgen Floege, MD, Director of the Division of Nephrology at RWTH Aachen University in Germany, reported that of 309 patients who completed the run-in phase, 94 (30%) achieved a reduction of proteinuria to <0.25 g/day on SUP. These patients were therefore “low-risk” for progression and did not enter the randomized treatment phase. After accounting for patients who dropped out or refused randomization, 80 patients were assigned to SUP and 82 to SUP plus immunosuppression with corticosteroids alone or in combination therapy. Equivalent proportions progressed regardless of immunosuppression

At 3 years there was no significant difference in the proportion of patients in each arm of the randomized phase of the trial whose disease progressed, defined as loss in estimated glomerular filtration rate (eGFR) of at least 15 mL/min compared to baseline. In the SUP-alone group, 24 patients (30%) had such an eGFR loss vs. 28 patients (34%) in the SUP plus immunosuppression group (p = 0.602).

A minority of patients in each arm of the randomized phase of the trial reached full clinical remission at 3 years, defined as proteinuria <0.2 g/day and an eGFR loss of <5 mL/min, although the group receiving immunosuppression did significantly better. Only 4 patients (5%) in the SUP arm were in remission versus 14 patients (17%) who achieved full clinical remission in the SUP plus immunosuppression arm (p = 0.011). “There seems to be a benefit of immunosuppression for some IgAN patients as indicated by the higher number of patients achieving full clinical remission,” Floege concluded. “However, this benefit is not accompanied by any detectable effect on functional loss,” as measured by eGFR decline. He noted that immunosuppressive treatment was accompanied by more serious adverse effects, including infections, diabetes, and weight gain.

The value of immunosuppression on top of SUP in the treatment of IgAN is controversial. Recent reports of the European Validation Study of the Oxford Classification of IgAN (VALIGA) trial indicated that immunosuppression was associated with significant reductions in proteinuria and in renal functional decline and with increased renal survival. The benefits were seen regardless of initial eGFR and with greater benefit at higher levels of proteinuria.

However, Floege noted that VALIGA was based on a retrospective analysis, “and it would not be the first time that a prospective, randomized study has refuted what was previously indicated by observational studies,” adding that STOP-IgAN is the largest randomized clinical trial that has addressed the question of immunosuppressive therapy in IgAN. A key difference between STOP-IgAN and previous trials also may be that STOP-IgAN achieved “very strict blood pressure control” during the run-in phase and throughout the ensuing 3 years of the trial, he said. Floege said an implication of STOP-IgAN for clinical practice is that “intensified, supportive therapy” with maximized antihypertensive and antiproteinuric medication “should always be provided initially.” If the desired outcomes are not achieved, then immunosuppression may be considered for patients with proteinuria up to 1.5 g/day. However, his results indicated that higher levels of proteinuria do not seem to benefit from immunosuppression, and these patients should therefore be spared the side effects of such treatment without an adequate prospect of success.

Delayed Graft Function Varies Between Transplantation Centers

Transplantation centers vary widely in their rates of delayed graft function (DGF) after deceased-donor kidney transplantation, reports a study in Transplantation. The study used data on more than 82,000 patients receiving deceased-donor kidney transplants between 2003 and 2012, drawn from the Scientific Registry of Transplant Recipients. The association between center characteristics and DGF was assessed, with adjustment for identified patient risk factors. Delayed graft function, defined as the need for dialysis during the first week after transplantation, occurred in 27.0 percent of patients. Across the 177 transplantation centers, DGF incidence ranged from 2.3 to 63.3 percent, with an interquartile range of 18.7 to 33.8 percent.

Center-level factors associated with a lower likelihood of DGF included the proportion of pre-emptive transplants, odds ratio (OR) 0.83 per 5 percent increment; and percentage of kidneys with cold ischemia time of 30 hours or longer, OR 0.95 per 5 percent increment. Factors associated with more DGF were the center’s proportion of donation of cardiac death, OR 1.12 per 5 percent increment; and imported kidneys, OR 1.06 per 5 percent increment.

In a combined patient-level and center-level logistic model, 41.8 percent of centers had a DGF incidence in line with the national median. The predicted incidence was above the median for 28.2 percent of centers and below the median for 29.9 percent. Although patient-level factors associated with DGF are well established, little is known about differences in DGF between transplantation centers. This study found significant variations in DGF between centers, even after adjustment for patient-level and center-level factors.

The authors note that their findings may reflect the subjective nature of the decision to begin dialysis in patients during the first week after transplantation [Orandi BJ, et al. Center-level variation in the development of delayed graft function after deceased donor kidney transplantation. Transplantation 2015; 99:997–1002].

APOL1 Genotype Affects Outcomes of Transplantation from African American Donors

The presence of APOL1 gene variants in African American kidney donors influences the risk of allograft failure after kidney transplantation, reports a study in American Journal of Transplantation. The researchers performed genotyping for apolipoprotein L1 (APO-L1) genotype G1 and G2 variants in DNA samples from African American deceased donors of kidneys recovered, transplanted, or both in Alabama and North Carolina. The association of APOL1 genotype findings with kidney transplantation outcomes at 55 centers was assessed. The findings were adjusted for recipient age, sex, and race/ethnicity; HLA matching; cold ischemia time; panel reactive antibody levels; and donor type. Analysis of 221 kidneys recovered in Alabama showed a trend toward shorter allograft survival in patients receiving kidneys with two APOL1 risk variants. For the total of 675 transplanted kidneys, allograft failure risk was significantly increased with APOL1 genotype, hazard ratio 2.26; and African American donor race/ethnicity, hazard ratio 1.60. For 99 kidneys with two APOL1 risk variants, allograft survival decreased from 89.3 percent at 1 year to 73.0 percent at 5 years to 54.5 percent at 10 years.

A previous single-center study reported lower renal allograft survival associated with APOL1 risk variants in African American deceased kidney donors. New findings in a large, multicenter sample of African American donors show an increased risk of allograft failure after transplantation of kidneys with two APOL1 nephropathy variants. These findings warrant consideration of rapidly genotyping deceased African American kidney donors for APOL1 risk variants at organ recovery and incorporation of results into allocation and informed-consent processes, the researchers write. [Freedman BI, et al. Apolipoprotein L1 gene variants in deceased organ donors are associated with renal allograft failure. Am J Transplant 2015; 15:1615–1622].