After spending a couple of years training in Boston, it is always a pleasure to go back, particularly in the summer. I recently had the opportunity to do just that for the American Transplant Congress from June 2nd through June 6th. Although I had a chance to enjoy the city, there was also a lot to learn at the symposia and abstract sessions. Like most thoracic transplant physicians, I like to take the opportunity to borrow from my below-the-diaphragm colleagues and think about which management strategies or novel immunosuppressives might be integrated into my practice. However, there also is a growing cardiac transplant presence at the meeting which I was asked to summarize for the ISHLT Links. What follows are some highlights from the cardiac sessions as well as a brief overview of what is new in immunosuppression from the remainder of the meeting.

Jon Kobashigawa presented the 24-month results of the A2310 study—a open-label, multicenter, randomized trial of 721 heart transplant recipients to one of three de novo immunosuppression regimens: everolimus 1.5mg plus reduced dose cyclosporine, everolimus 3.0mg plus reduced dose cyclosporine or standard dose cyclosporine with 3gm of mycophenolate. Higher mortality in the everolimus 3mg arm led to discontinuation of that regimen. At 24 months the composite endpoint (biopsy–proven rejection, rejection with hemodynamic compromise, death, graft loss, or retransplant) in the everolimus arm (39.4%) was non-inferior compared to the cyclosporine arm (41.3%). The rates of the individual components of the composite endpoint were similar between groups. The mean difference in renal function as assessed by MDRD was 6.5 mL.min in favor of the standard cyclosporine group, however the achieved cyclosporine levels in the everolimus arm were higher than the target levels, which may have contributed to the lack of a renal benefit in the everolimus group.

There was also a separate report on safety events of interest in the A2310 study. There were few new adverse events in either the low dose everolimus arm or the standard dose cyclosporine arm after the first post-transplant year. There were few new cases of nonsternal wound dehiscence or pericardial effusions in either arm. Between months 12 and 24, no patient in either group developed new proteinuria, but the rate of new occurrence of hyperlipidemia was higher in the everolimus group than the cyclosporine group, 7.5% v. 4.5% respectively.

The long-term outcomes of the Tacrolimus In Combination, Tacrolimus Alone Compared (TICTAC) trial was presented in which 150 patients from two centers were randomized to tacrolimus monotherapy versus tacrolimus plus mycophenolate. Survival at 1, 3, and 5 years was 97%, 90%, and 81% in the tacrolimus monotherapy group and 99%, 96%, and 91% in the tacrolimus/MMF group, p=0.11. There was also no difference in freedom from vasculopathy in the monotherapy group: 100%, 96%, and 88% versus the tacrolimus/MMF group 100%, 97%, 94%, p=0.18. The four year cancer-free survival after alemtuzumab induction therapy was presented; there was no difference between those who received alemtuzumab 92.1% v. thymoglobulin 92.9% v. no induction 89.5%, p=0.50. The most common cancer was squamous cell cancers in all groups and when nonmelanotic skin cancers were excluded, non-small cell lung cancer was the most common malignancy.
The Cedars group presented data on older donors in older recipients. They reviewed 380 patients who were age 60 or greater at transplant, 327 had donors less than 50 years old and were compared to 53 patients with donors aged 50 or greater. The 5 year actuarial survival was superior for those with younger versus older donors: 85% v. 57%, p<0.001 as was the 5 year freedom from major cardiac events 92% v. 83%, p=0.03. However 1 year freedom from treated rejection did not differ between groups 90% v. 90%, p=0.96. The Eurotransplant donor risk score was applied to patients over 13 years at the University of Vienna. Those with higher scores (>=17 points) had a higher rate of primary graft dysfunction compared to those with lower scores (< 17 points): 37.5% v. 21.9%, p=0.015. Those with higher scores also had worse 30 day (73.5% v. 88%, p=0.004) and 3 year survival (63.3% v. 78.2%, p=0.018). Lastly an analysis of the UNOS database demonstrated worse waitlist survival for Heart/Lung, Heart/Liver, and Heart/Kidney patients, although the survival benefit for Heart/Liver and Heart/Kidney patients was greater than that for Heart-alone patients listed as 1b, but over 80% of the combined organ transplants were listed as status 2. This study questioned whether current status criteria should be amended for those listed for a liver and kidney, in addition to a heart.

The development of DSA was the topic of two abstracts retrospectively analyzing de novo DSA in patients over a 13 year period at Harefield Hospital, exclusive of those who had pretransplant DSA or who did not survive one year. A total of 243 patients were included and 56 developed de novo DSA (using an MFI cutoff of 1000). About 8% of patients developed DSA in the first year post-transplant and about 20% by 3 years. The only multivariate factors predictive of de novo DSA development were having 6 or more HLA mismatches and male recipients who received a male donor. From the date the de novo DSA was detected, the rate of graft loss at 1, 3 and 5 years was 20%, 24%, and 36% respectively. However those with IgG3 isotype DSA had the highest rate of graft loss at those same time periods: 29%, 35%, and 55%. Overall for those who develop any de novo DSA, nearly 40% will have died or developed vasculopathy at 5 years. The Cedars group found no difference in 3 year survival among those with no antibody (n=158) versus those with a positive DSA with an MFI < 5000 (n=18) or DSA with an MFI > 5000 (n=9), 87% v. 78% v. 78%, p=0.43. However, there were significant differences between those with no antibody, low MFI DSA and high MFI DSA with respect to one year freedom from treated cellular rejection (96% v. 100% v. 78%, p=0.01) and freedom from treated AMR (97% v. 94% v. 78%, p=0.005).

The AST presents a good opportunity to see what is new in noncardiac solid organ transplantation and what drugs are in the pipeline. While an exhaustive survey is beyond the scope of this Links update, I will present a broad overview of a number of presentations on novel immunosuppression. The renal experience with belatacept, which blocks T-cell co-stimulation, in two trials BENEFIT and BENEFIT-EXT was reviewed. All patients received basiliximab induction, mycophenolate, and steroids. Patients were randomized 1:1:1 to receive a more intense
or less intense belatacept regimen or cyclosporine. Maintenance therapy with belatacept was given by monthly infusions. Overall results demonstrated that the belatacept groups had similar patient and graft survival and better renal function, despite having a higher early incidence of acute rejection. There were also metabolic advantages to the belatacept regimen with better blood pressure and lipid control. Interestingly there was also less de novo antibody formation, whether this was due to the inhibition of the production of antibody or patients receiving more consistent immunosuppression, given that they had to have supervised monthly infusions, is unclear.

Other than a higher incidence of early rejection in the belatacept group there was more PTLD, particularly in the EBV(R-/-D+) patients, however there was no differences in the rates of CMV or BK. Additionally, there are issues of logistics, cost, and regulatory burdens with belatacept due to the requirement for intermittent intravenous dosing.

The JAK3 inhibitor, tofacitinib, is being investigated in solid organ transplant as well as rheumatoid arthritis, psoriasis, and Crohn’s disease. In a phase Ib trial of a higher and lower intensity tofacitinib versus cyclosporine on a background of basiliximab induction, mycophenolate, and steroids found similar rates of BPAR, superior GFR, and less chronic allograft nephropathy in the tofacitinib groups. This study also demonstrated a greater incidence of infection, including CMV and BK as well as numerically more cases of PTLD with tofacitinib. However, those who had tofacitinib exposure below the median had similar rates of infection, CMV, and PTLD with comparable BPAR rates to the cyclosporine group.

Sotrastaurin is a protein kinase C inhibitor which results in a calcineurin-independent blockade of T-cell activation. On a background of basiliximab induction, mycophenolate, and steroids patients were randomized 1:2 to tacrolimus or sotrastaurin. The study was terminated early because the sotrastaurin group had a higher incidence of the primary endpoint of BPAR, graft loss, death or lost to follow-up at 3 months (25.7% v. 4.5%, p=0.001), mostly due to a higher rates of BPAR. However, eGFR was better in the sotrastaurin compared to tacrolimus.

Other novel agents in development include Diannexin, a recombinant form of human Annexin V, which was developed to prevent ischemia-reperfusion injury. In preliminary studies of marginal kidney transplants the early GFR was better in the Diannexin group. The hypoxia and oxidative stress of reperfusion induces p53 expression which results in apoptosis, the drug QPI-1002 is a synthetic RNA which temporarily inhibits p53 expression. There is not yet human data for QPI-1002. Another drug, ASKP1240, a human monoclonal antibody to CD40 is being assessed in nonhuman primate studies. Lastly, TOL101 is a murine monoclonal antibody to the αβ receptor of CD3+ T-cells which down regulates the T-cell receptor and is in phase I/II development.

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References: