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# EMERGING

## PRACTICAL AND CLINICAL IMPLICATIONS OF EMERGING CNI-FREE IMMUNOSUPPRESSIVE REGIMENS

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***Presented at the American Transplant Congress 2008***
***Toronto, Ontario***

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### LEARNING OBJECTIVES

Following completion of the CE program, the audience will be able to explain how immunosuppressive regimens that target non-calcineurin pathways

- Reduce the risk of nephrotoxicity and renal dysfunction
- Improve the potential for enhanced long-term outcomes
- Impact the clinical management of transplant patients

### TARGET AUDIENCE

This program is designed to educate medical professionals involved in the management of solid organ transplant patients including: surgeons, physicians, pharmacists, coordinators and nurses.

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### ACKNOWLEDGEMENT

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## Needs Assessment

One of the great dilemmas in modern transplantation is the need to circumvent the alloimmune response by administering immunosuppressive agents that produce long-term, potentially serious adverse events. Indeed, despite great strides in investigating, approving and utilizing new immunosuppressants in the clinic, the last 2 decades have witnessed significant graft and patient loss due in part to the adverse effects of immunosuppressive agents on renal function and cardiovascular health.[1]

Immunosuppressants that target the calcineurin pathway of T cell activation, the calcineurin inhibitors (CNIs), are widely believed to be principal mediators of the adverse events burden.[2, 3] However, strategies to minimize their use have been met with limited success, due in part to a significantly increased risk of inadequate immunosuppression and therefore elevated risk of acute rejection.[4]

Calcineurin activation is a necessary primary step in T cell activation, triggering subsequent molecular events that result in cytokine production and T cell proliferation.[5] Costimulation, one of the earlier downstream events in the cascade, ensures that the allopeptide-TcR/MHC binding that triggered calcineurin activation produces T cell differentiation and proliferation as opposed to anergy.[6, 7]

Transplant professionals are well acquainted with the double-edged effects of CNI-based immunosuppressive regimens. However, there is a need to raise awareness concerning emerging alternative strategies. The American Transplant Congress, held in Toronto, Canada, May 31-June 4, 2008, provided the opportunity to exchange new scientific and clinical information relevant to immunosuppression targeting the costimulatory pathway of T cell activation. "Immunosuppression: Possible — Practical and Clinical Implications of Emerging Calcineurin Inhibitor-Free Immunosuppressive Regimens" was an evening satellite symposium devoted to a review of the limitations and benefits of CNI-based regimens, and a discussion of emerging therapy with belatacept, a costimulation inhibitor. The present Newsletter summarizes the state-of-the-art content presented by the three expert faculty members during the symposium.

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**THE SYMPOSIUM POSED THREE BROAD QUESTIONS CONCERNING CURRENT AND FUTURE MAINTENANCE IMMUNOSUPPRESSIVE STRATEGIES, OUTLINED BELOW.**

| Dr. A Ojo | Dr. H-U Meier-Kriesche | Dr. ES Woodle |
|---|---|---|
| How do the principal toxicities associated with current maintenance immunosuppression affect long-term graft survival? → | How successful have we been in our attempts to spare CNIs? → | How would the entry of costimulatory blockade into the maintenance immunosuppression armamentarium change the management of our transplant patients? |

## INTRODUCTION: ADOPTING CNI-FREE MAINTENANCE IMMUNOSUPPRESSION: CLINICAL AND PATIENT MANAGEMENT CONSIDERATIONS

Dr. Ojo began by crediting CNIs with an impressive reduction in the incidence of acute rejection over the first year following renal transplantation.[1] He then discussed the clinical evidence associating CNI-related toxicities with compromised kidney allograft survival, stressing that chronic nephrotoxicity due to CNIs is virtually universal following kidney transplantation.[8] Finally, he reviewed the evidence linking chronic kidney dysfunction, cardiovascular events, and eventual graft loss.[9]

To counterpoint the dilemma, Dr. Meier-Kriesche discussed the results of recent attempts to limit the use of CNIs as a means of sparing toxicities.[2] Reviewing the evidence for long-term kidney graft attrition, Dr. Meier-Kriesche concluded that multiple factors affect graft outcome in the long-term, thereby complicating a determination of the proportional impact of CNIs.[2, 3, 10-12] He also cautioned that CNI minimization strategies have not demonstrated uniform benefit. Therefore, if optimizing outcomes will depend on identifying and utilizing alternative immunosuppressive strategies, they must retain the immunologic benefit of CNIs, while reducing the burden of adverse events.

Finally, Dr. Woodle presented the rationale for targeting costimulation to achieve immunosuppression. While early attempts to target the costimulatory pathway in nonhuman primate models of transplantation were focused on the achievement of transplant tolerance, recent strategies highlight the potential to affect safe long-term maintenance immunosuppression through costimulatory blockade.[7]

Investigation of the costimulatory pathway as a target of immunosuppression has led to the development of the CD28 blocker belatacept. The results of Phase 2 clinical trials in solid organ transplantation with this agent suggest that targeting the costimulatory pathway may indeed provide effective immunosuppression, with the potential to bypass the calcineurin pathway and the toxicities associated with CNIs. However, important questions focused on a shift in the clinical maintenance and follow up routine remain before costimulatory blockade is adopted into transplantation clinical practice.

## PART I: THE IMPORTANCE OF RENAL FUNCTION ON LONG-TERM GRAFT AND PATIENT SURVIVAL AFTER TRANSPLANTATION

**Akinlolu Ojo, MD, PhD**
University of Michigan Medical School

***How do the principal toxicities associated with current maintenance immunosuppression affect long-term graft survival?***

Significant reduction in the incidence of acute rejection during the first posttransplant year has been observed in recent years, due to the maintenance use of CNIs in combination with mycophenolate mofetil (MMF) **(FIGURE 1)**. However, this impressive improvement in acute rejection has failed to translate into improved longevity of transplant patients. Indeed, since 1995, the average lifespan of kidney allograft recipients has been declining **(FIGURE 2)**.

FIGURE 1: INCIDENCE OF ACUTE REJECTION AT 1 YEAR IN KIDNEY TRANSPLANT RECIPIENTS, 2000-2005[1]

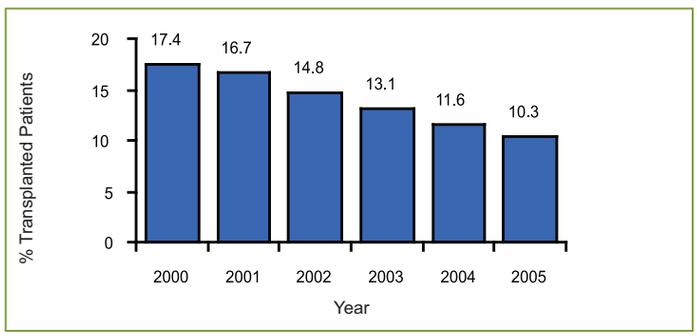
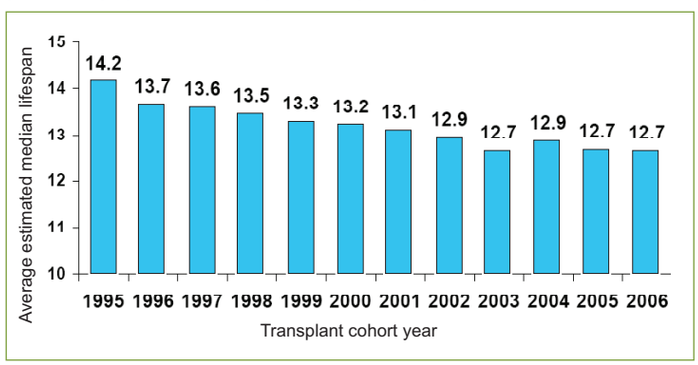


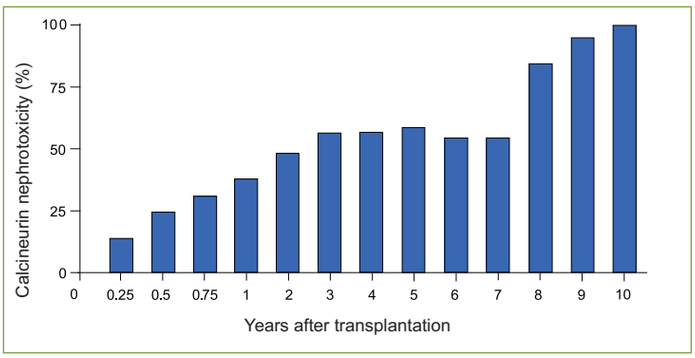

FIGURE 2: DECLINE IN AVERAGE POSTTRANSPLANT LIFESPAN AMONG STANDARD CRITERIA DONOR KDINEY TRANSPLANT RECIPIENTS[1]




While multiple factors are implicated in posttransplant mortality, progressive nephrotoxicity and the influence of renal dysfunction on cardiovascular status are two likely suspects. In turn, the class of CNI immunosuppressive agents are known to be directly nephrotoxic.

Histologic evidence of cyclosporine-associated nephrotoxicity has been documented in nearly 100% of kidney-pancreas recipients by 10 years of follow up **(FIGURE 3)**.[8] The histologic pattern of kidney damage is mirrored by the loss of function, suggesting that renal insufficiency is cumulative over time following transplantation. While the rate of decline in kidney function appears to be stabilizing in the most current transplant era, the annual loss of slope of GFR of 1.4 ± 10.9 mL/min/1.73m$^2$ is evidence that there is significant room for improvement.[13]

FIGURE 3: PROGRESSION OF CNI NEPHROTOXICITY[8]




The mechanisms of CNI-associated renal toxicity have been investigated. Exposure to CsA is accompanied by intense vasoconstriction in the renal capillary bed and elevated systemic vascular resistance manifesting as hypertension.[14] Progressive gradual deterioration of GFR is observed over time along with a steady decline in renal blood flow (RBF). After a critical reduction in nephron mass from chronic glomerular ischemia, the rate of loss of GFR exceeds the decrement in RBF. At this point, even restoration of RBF to normal is unlikely to mitigate the progressive loss of renal function secondary to maladaptive nephron hyperfiltration in the remnant functioning renal mass. Thus, the timing of the elimination of an agent that is causing glomerular ischemia (such as a CNI) is of critical importance. Kidney sparing is likely to be realized if the CNI is eliminated from the immunosuppressive regimen between 3 and 6 months after transplantation, before the nephron loss reaches the "point of no return".

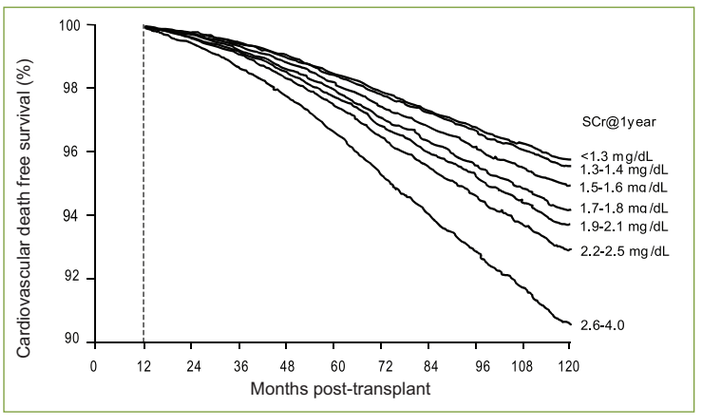
As suggested above, the consequences of nephrotoxicity extend beyond allograft function. Compared to patients with preserved renal function, kidney transplant recipients with renal insufficiency are at greater risk of cardiovascular death. At 1 year posttransplant, renal function is strongly associated with both the incidence and risk of cardiovascular death independent of the many other known risk factors for cardiovascular disease.[9] A significant and progressive increase in the risk for cardiovascular death has been observed at serum creatinine values above 1.5 mg/dL **(FIGURE 4)**. Indeed, death with a functioning graft (DWF) is the most common cause of graft loss in kidney transplant recipients beyond the first year after transplantation, and cardiovascular disease accounts for 50% of DWF.[15, 16]

## Summary: Part I

Evidence to date suggests that preserved kidney function is likely to extend posttransplant patient survival.

Therefore, there is a compelling need for maintenance immunosuppressive therapy that optimizes renal function over the long-term.

FIGURE 4: RENAL FUNCTION AND CARDIOVASCULAR RISK IN KIDNEY TRANSPLANT RECIPIENTS[9]




## PART II: IMMUNOSUPPRESSIVE REGIMENS TO PRESERVE RENAL FUNCTION: WHAT HAS WORKED AND WHAT HAS NOT WORKED

**Herwig-Ulf Meier-Kriesche, MD**
University of Florida College of Medicine

### *How successful have we been in our attempts to spare CNIs?*

Not surprisingly, the impact of CNIs on long-term renal function has sparked intensive investigation of CNI sparing immunosuppressive regimens. The earliest trial of CNI avoidance resulted in an unacceptably high acute rejection incidence of 53%, forcing investigators to turn attention to less aggressive CNI minimization strategies.[2, 17, 18] This experience reinforced the need to balance reduction in the adverse events burden with the preservation of immune modulation.

The CAESAR clinical trial compared cyclosporine withdrawal by 6 months under daclizumab induction therapy with low dose cyclosporine therapy under the same induction regimen. While the results were somewhat more promising than those of the avoidance trial, the incidence of acute rejection in the withdrawal arm was still 38%, compared to 25.4% in the low dose treatment group ($P$=0.027).[19] Notably, analysis of renal function revealed no improvement in the withdrawal arm compared to groups treated with low or standard dose cyclosporine. This experience suggested that CNIs are not the sole risk factors for deteriorating renal function following transplantation.

Recent analysis of the transplant registry suggests that keeping CNIs on board may in fact optimize renal function and renal allograft survival over time. Indeed, the best graft survival over 5 years occurred among patients maintained on regimens containing cyclosporine or tacrolimus **(FIGURE 5)**.[20]

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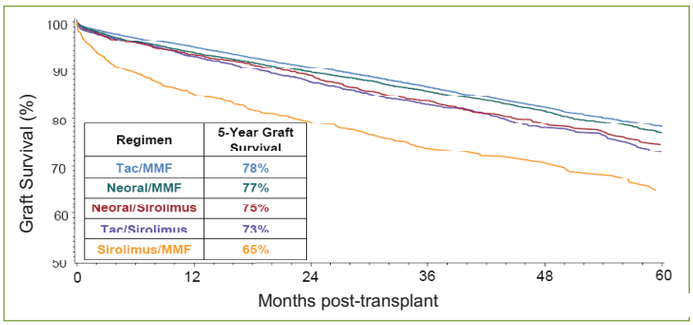
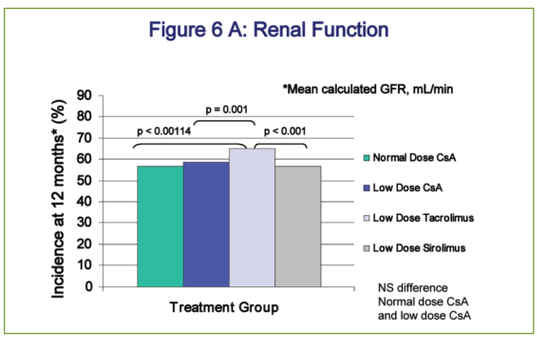
FIGURE 5: OPTIMAL OVERALL GRAFT SURVIVAL ASSOCIATED WITH CNI USE



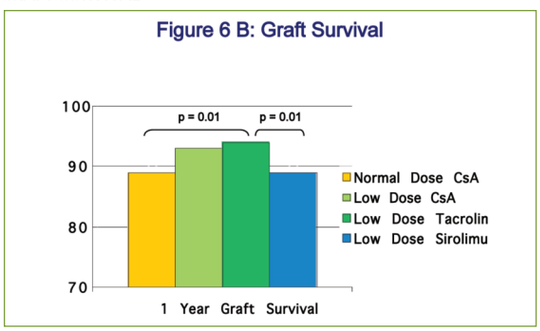

Finally, head-to-head comparison of regimens based on low dose tacrolimus or cyclosporine with a standard dose cyclosporine regimen and a regimen containing sirolimus but no CNI in the SYMPHONY clinical trial corroborate the registry results, at least over the first year of follow up. The low dose tacrolimus-based regimen resulted in the lowest incidence of acute rejection (12.3%), the highest estimated GFR (65.4 mL/min), and the highest graft survival rate at 1 year of follow up **(FIGURE 6)**.[21] It is important to note that all patients in the SYMPHONY clinical trial received MMF, and all except those randomized to the standard dose cyclosporine group were administered daclizumab induction therapy.

FIGURE 6: OPTIMAL SHORT-TERM RENAL FUNCTION AND GRAFT SURVIVAL UNDER CNI-BASED IMMUNOSUPPRESSION[21]

A: RENAL FUNCTION




B: GRAFT SURVIVAL




The statistical significance of these differences appears to have been lost at 2 and 3 years of follow up. At 3 years, estimated GFR was 69 mL/min among patients maintained on low dose tacrolimus, and between 64 and 66 mL/min in the alternate treatment arms, with no statistically significant differences among groups. Similarly, graft survival ranged between 87 and 89%.[22, 23]

These experiences clearly demonstrate that eliminating or significantly reducing exposure to immunosuppression is not the best approach to achieve excellent long-term outcomes. Rather, optimal survival depends on the identification, investigation and utilization of new maintenance immunosuppressive strategies that achieve both effective immune modulation and a minimum of adverse physiologic events.

## Summary: Part II

Investigations of immunosuppressive drugs in various combinations have failed to validate the concept of *de novo* CNI-free immunosuppression.

While the best short-term acute rejection and renal function results are obtained under CNI-based immunosuppression, long-term toxicities continue to fuel the search for alternate strategies that both modulate the alloimmune response and optimize long-term function and survival.

## PART III: PRACTICAL IMPLICATIONS FOR EMERGING CALCINEURIN INHIBITOR-FREE REGIMENS

**E. Steve Woodle, MD, FACS**
University of Cincinnati College of Medicine

### *How would the entry of costimulatory blockade into the maintenance immunosuppression armamentarium change the management of our transplant patients?*

The alloimmune response is the product of a series of molecular signals activated by the binding of allopeptide to antigen presenting cell (APC)-bound MHC, and subsequent presentation to allospecific T cell receptors.[5] This primary signal eventually results in the activation of calcineurin and the mobilization of cytokine-activating transcription factors to the T cell nucleus. However, this signal is insufficient to trigger full T cell activation. Costimulation, mediated by the T cell CD28-APC CD80/CD86 pathway, as well as others, is required to ensure that the initial signal produces stimulatory rather than anergic consequences.

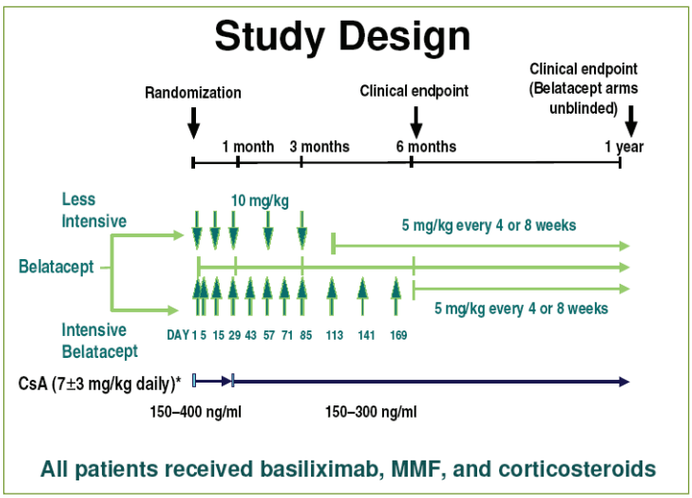
The costimulation pathway has been investigated as a potential adjunct or alternative to calcineurin inhibition, to achieve effective and safe transplant immunosuppression. CTLA-4, a costimulatory molecule expressed shortly following T cell activation, behaves as a natural immunomodulator by down regulating the T cell CD28-APC CD80/CD86 interaction.[7] With higher avidity for CD86 than CD28, CTLA-4 effectively prevents costimulation, encouraging T cell anergy. Investigation of this pathway led to the development of CTLA-4Ig (abatacept), a fusion product of CTLA-4 and the Fc portion of human IgG1, to interrupt the costimulatory pathway.

Early attempts to block costimulation with CTLA-4Ig in animal models of transplantation resulted in promising limitation of acute rejection, and evidence of tolerance.[7] However, while a reduction in acute rejection could be duplicated in some large animal models, tolerance could not.[24] Mutagenesis produced a new molecule, belatacept, with mutations at sites L104 A29 resulting in a 4-fold increased avidity for CD86, twice the avidity for CD80, and one log increased inhibition of T cell activation *in vitro*.[25]

**Belatacept clinical trial.** Belatacept treatment of nonhuman primates resulted in significant reduction in acute rejection incidence, and the molecule was selected for clinical development.[25] The results of a large Phase 2 clinical trial of belatacept provide cautious optimism for the ability of the agent to limit acute rejection within a tolerable burden of adverse events.

The Phase 2 trial of belatacept was designed to compare the efficacy and safety of belatcept treatment, at a less intensive (LI), or more intensive (I) dosing regimen, to cyclosporine (CsA) **(FIGURE 7)**.[26]

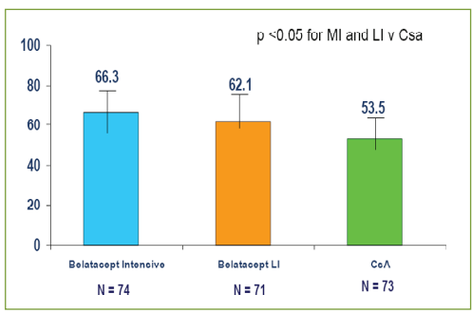
FIGURE 7: BELATACEPT PHASE 2 CLINICAL TRIAL DESIGN




**Efficacy.** At 12 months of follow up, acute rejection was well controlled in all treatment arms (7%, 6% and 8% in I, LI and CsA treatment groups, respectively). However, kidney function, as measured by GFR, was significantly better among patients treated with belatacept, and there was a reduced incidence of chronic allograft nephropathy (CAN) **(FIGURE 8)**.[26] Results at 48 months of a long-term extension of the study suggest that belatacept continues to support improved renal function **(FIGURE 9)**.

FIGURE 8: PHASE 2 TRIAL OF COSTIMULATORY BLOCKADE WITH BELATACEPT — KIDNEY FUNCTION AND CHRONIC ALLOGRAFT NEPHROPATHY

A. MEASURED GFR




B. CHRONIC ALLOGRAFT NEPHROPATHY

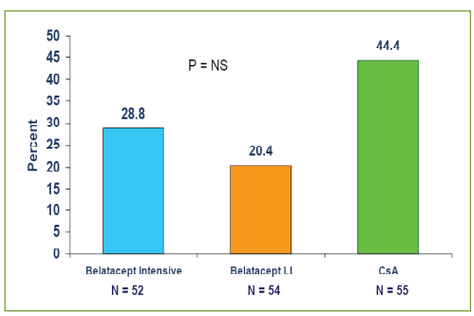
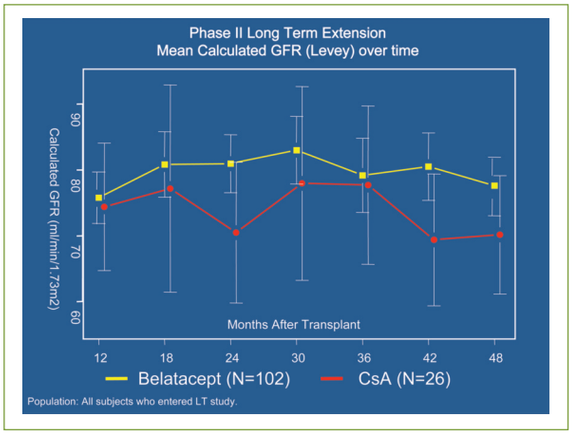



FIGURE 9: PHASE 2 TRIAL OF COSTIMULATORY BLOCKADE WITH BELATACEPT – LONG-TERM RENAL FUNCTION




**Safety.** The trial also revealed a significantly lower incidence of new onset diabetes (1% in each of the belatacept treatment arms vs. 8% for CsA; *P*=0.04), and a significantly reduced requirement for lipid lowering agents (LI–32%, I–36%, and CsA 53%; *P*=0.003) among patients randomized to belatacept therapy.[26] Despite the early development of 3 cases of posttransplant lymphoproliferative disorder (PTLD) in the belatacept intensive treatment arm, further follow up has revealed no increased risk of PTLD associated with belatacept therapy (rate per 100 pt-years among belatacept or CsA-treated patients = 0.7, with 95% CI = (0.1-1.9) and (0.0-3.7), respectively).

The results of the Phase 2 study experience with belatacept are promising, with respect to efficacy, renal safety and adverse events burden. However, patient follow up time is relatively short, and it must be noted that, as in other non-CNI immunosuppression clinical trials, enrollment was restricted to patients at low-to-moderate risk. In addition, only the outcome of the several Phase 3 trials underway (BENEFIT, CNI Conversion; ITN Tolerance; Early Corticosteroid Withdrawal) can provide a definitive answer to the efficacy and safety questions first posed.

**Potential for change in treatment paradigm.** If successful, costimulation blockade presents a new paradigm for the management of maintenance immunosuppression over the long-term. While patients will clearly still self-administer daily oral medications including the immunosuppressant MMF, they will also require clinic visits as frequently as once monthly to receive a principal drug in the immunosuppressive regimen. The implications for adherence, closer follow up of metabolic status, the logistics of clinic management, and clinic costs have yet to be evaluated. In addition, a once monthly infusion schedule of potentially large populations of transplant patients poses significant issues for nursing care.

## Summary: Part III

Belatacept is the first costimulation blockade immunosuppressive agent to be trialed in clinical transplantation.

12-month results of the Phase 2 clinical trial of belatacept in kidney transplantation provided evidence of

- Effective control of acute rejection
- Superior control of chronic allograft nephropathy
- Improved renal function
- Acceptable metabolic safety

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**PART IV: REMAINING QUESTIONS**

The movement of costimulatory blockade to transplantation clinical practice prompts several unanswered questions. We have already pointed out that clinical trials without CNIs have routinely enrolled patients at low-to-moderate immunologic risk. However, the greatest need to improve outcomes exists among populations of historically high-risk patients, including African Americans, recipients of extended donor organs, and retransplant recipients. A Phase 3 clinical trial designed to evaluate outcomes in high-risk recipients of extended criteria donor kidneys is currently on-going (the BENEFIT-EXT study).

Clinical trial design continues to challenge our interpretation of study results in the current era of transplantation. While most immunosuppressive agents used in transplantation are approved for the indication, it is estimated that 95% of transplant patients receive combinations of immunosuppressive agents in off-label regimens. This is clearly a reflection of the simultaneous regulatory development of tacrolimus, microemulsion cyclosporine, MMF, and sirolimus, which could not be combined in optimal regimens in registration clinical trials. Since the time of initial approval, FDA-regulated labels have not been updated to reflect modern drug regimens.

We are therefore forced to design immunosuppressive regimens without benefit of appropriate comparator clinical trials. One compelling question concerning belatacept, or any other novel immunosuppressant, is how that agent performs against standard-of-care CNI-based therapy, which currently consists, at the majority of centers, of tacrolimus plus MMF.[1] Clearly, we cannot answer this question within the current regulatory environment. While we may partially extrapolate the answer from the SYMPHONY clinical trial, which showed equivalent outcomes for cyclosporine- and tacrolimus-based therapy at 2 and 3 years of follow up, there is no substitute for head-to-head trials.

Long-term outcomes in transplantation are the result of a complex mix of pretransplant risk factors, donor organ history, recipient-donor compatibility, and posttransplant surgical and medical management. Agents like belatacept that require in-clinic administration offer us the opportunity to more closely manage our patients' progress over the years. Perhaps this itself is the best means of ensuring excellent long-term outcomes under a new maintenance paradigm.

To view a video of this symposium please visit www.CECentral.com/ATC2008

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