Findings: American Transplant Congress

Proteasome Inhibitor Reverses Major Cause of Graft Loss

By Daniel M. Keller

The proteasome inhibitor bortezomib reverses early and late antibody-mediated rejection (AMR), a major cause of solid organ transplant loss. The drug opens up a new avenue for specifically targeting plasma cells, the cells that produce antibodies.

Speaking at the American Transplant Congress in Philadelphia in May, Steve Woodle, MD, professor and chairman of surgery and chief of the division of transplant surgery at the University of Cincinnati in Ohio, explained that AMR affects all solid organ transplants. "If you look at the reasons why people lose their grafts, there's evidence to suggest that the predominant mechanism is antibody-mediated," he said. "The therapeutic paradigm is to target the plasma cell, and this approach is actually the first plasma cell–targeted therapy that's been used in humans, and so I think that's the significance."

Reporting on 96 episodes of AMR occurring in 81 recipients of kidney transplants, Woodle said that bortezomib effectively reversed AMR and was associated with graft survival and histologic improvement in the majority of patients. In the past decade, AMR has been seen as an important contributor to acute and chronic rejection and graft loss. It typically does not respond to antirejection therapies aimed against T cell–mediated immunity.

In this multicenter study, patients received a single dose of rituximab, an anti–B cell drug, on day 1, followed by four doses of bortezomib on days 1, 4, 7, and 10, preceded each time by plasmapheresis. Further plasmapheresis occurred on days 14, 16, and 18 to remove existing antibodies and allow quantification of antibody production from residual B cell clones. The immunodominant anti-HLA antibodies directed against donor-specific antigens were identified.

"Patient survival has been excellent, to date almost 99 percent," Woodle said. "The time posttransplant to rejection was a median of 11.9 months, a mean of 30 months, with a range from early on to patients 10 years out or more."

About one third of patients experienced early AMR and the rest late AMR, averaging about 5 years after transplant for his institution and 2.5–3 years at the other participating centers. Most of the immunodominant donor-specific antibodies were about equally divided against class I or class II major histocompatibility complex antigens in early rejection. "About 70 percent of those that were biopsied were improved," Woodle said.

During late AMR, antibodies were predominantly directed against class II antigens, especially against DQ specificities. Histologic improvement during late AMR was slightly lower than during early episodes.

Graft survival was about 80–90 percent in early AMR and 67–76 percent in late AMR. Patient survival has been 100 percent for early AMR and about 75 percent for late episodes. Use of the treatment protocol was associated with significant declines in the amount of circulating immunodominant donor-specific antibodies.

Serum creatinine levels improved more after treatment for early AMR than when patients were treated during late AMR episodes. "Late rejection creatinines are higher in general as one might expect, and they don't show improvement to baseline," Woodle said. "They wind up around 2 mg/dL rather than 1.2–1.5 [mg/dL]."

Peripheral neuropathy is probably the most dose-limiting side effect with bortezomib. Woodle said only about 2–3 percent of patients experienced grade 3 neuropathy, meaning that they had painful neuropathy requiring narcotics. This rate is similar to that seen when bortezomib is used in the oncology setting to treat multiple myeloma or relapsed mantle cell lymphoma, the only indications for which it is approved by the U.S. Food and Drug Administration.

Some viral infections occurred in early AMR but responded to antiviral therapy and reduction in immunosuppressive drugs. During late AMR, the rate of opportunistic infections was lower, at about 4 percent. No deaths were related to opportunistic infections, and no malignancies occurred during the study.

"Results with proteasome inhibitor therapy differ between early and late antibody-mediated rejection," Woodle told the audience. "Patient survival has been excellent. Overall graft survival is comparable or higher than reports with other therapies.

"Graft survival is lower with a late AMR. This is typical of what's been reported with IVIG [intravenous immunoglobulin] and other types of therapies," he noted. "The toxicities are acceptable, and the opportunistic infection and malignancy rates are also acceptable." In comparison with the use of bortezomib in the oncology setting to treat multiple myeloma, he said that transplant patients with AMR were exposed to relatively low levels of the drug.

Proteasome inhibitors are "fundamentally different than IVIG, where the primary mechanism of action is not known or is not well sorted out," Woodle told *ASN Kidney News*. He expects to see the development of more drugs and combinations of drugs over the next several years to target the humoral immune response, and he compares today with the era 25 years ago in which T cell–directed therapies came about.

"Early acute rejection is much easier to control and address. Delayed antibody-mediated rejection that is switching into the chronic state is much more difficult to reverse, and the damage is already done and can be somewhat stopped but not reversed," said session moderator Tomasz Kozlowski, MD, assistant professor of surgery at the University of North Carolina at Chapel Hill.

Kozlowski said that he found the protocol used in the study "very exciting," and he expects that future studies will show "which component of this protocol is really contributing to the success and how we actually define the success."

Sexually Transmitted Infection: New Category of High-Risk Organ Donors

By Daniel M. Keller

Sexually transmitted infection (STI) could be considered a high-risk category for HIV transmission through organ donation. But hemophilia should now be dropped as a risk category, given the low incidence of HIV in that population, according to a study presented at the American Transplant Congress in Philadelphia in May.

The U.S. Centers for Disease Control and Prevention (CDC) issued classifications of high-risk organ donors in 1994, but the epidemiology of certain infections has changed since then. Current evidence shows that STI could now be considered a high-risk category, given the high incidence and prevalence of HIV among this population. But given the very low 1 in 100,000 incidence of HIV among people with hemophilia, it should be dropped as a high-risk category, said Lauren Kucirka, ScM, an epidemiologist in the department of surgery at the Johns Hopkins University School of Medicine in Baltimore.

The CDC currently categorizes potential donors as being at high risk on the basis of seven behaviors or circumstances. These individuals include men who have sex with men, injection drug users, people with hemophilia, commercial sex workers, people who have high-risk sex (that is, with people in any of the foregoing groups), people who have been exposed to HIV through blood, and people who are incarcerated.

By these criteria, about 9 percent of donors from whom at least one organ is recovered are classified as being at high risk, and these organs are 26 percent more likely to be discarded than are those from donors not at high risk. Kucirka noted that the CDC guidelines have several limitations: they were designed in 1994, before the advent of highly active antiretroviral therapy; they were aimed in part at HIV but have been extended to hepatitis C virus (HCV) infection; and although they were designed to identify donors at risk of prevalence infection, the real risk from HIV is from incident infection. In the case of hemophilia, for example, the prevalence of HIV is high among people who received transfusions in the 1980s, but because of tests to screen blood the incidence of new infections is low.

To investigate potential new high-risk categories, Kucirka and colleagues performed a systematic review of the literature on the incidence and prevalence of HIV and HCV from 1995 through 2008, as well as a meta-analysis. They identified 272 eligible abstracts for HIV estimates and 218 for HCV estimates.

Window period

A "window period" exists between the time of an infection and when it is detectable by laboratory methods. All donors are screened for infectious diseases, but they will falsely test negative if they are in the window period and may then transmit an infection to one or more recipients. "The window period using nucleic acid testing for diseases like HIV and hepatitis C is about a week," Kucirka said.

From the abstracts, the investigators were able to calculate a "risk of window-period infection" for HIV. For the current CDC categories, "the incidence ranged from two infections per 100 person-years for injection drug users to less than 1 per 10,000 person-years for hemophiliacs," she said.

On the basis of a review of the abstracted data, the authors discerned subgroups of the population with a high incidence of HIV or HCV. Body piercings, tattoos, or intranasal cocaine use did not appear to confer any increased incidence in comparison with control individuals from the same study populations.

"And finally we looked at STI," Kucirka said. "So we found among those who were positive for [any] STI a pooled incidence of 1.7 per 100 person-years, which was similar to the incidence in men who have sex with men and injection drug users and would result in an expected number of 4.2 window-period HIV infections per 10,000 donors." Compared with their peers from the same study population, people with STIs had about twice the prevalence and twice the relative incidence of a window-period HIV infection.

"Addition of new categories should be approached with caution, particularly in light of the high discard rate when a donor is classified as at high risk," Kucirka advised. Nonetheless, STI could be considered a potential high-risk category, given the high incidence and prevalence of HIV infection in this category. But given the very low incidence among people with hemophilia, this category "could potentially be dropped," she said.

The CDC is currently formulating new guidelines and will put them out for comment soon.

"We're operating based on some assumptions that were made in 1994 that were clearly obsolete at this point and inappropriate in some settings and don't reflect either the available testing or the changing demographics of blood-borne pathogens like HIV and hepatitis C and hepatitis B," said Emily Blumberg, MD, professor of medicine and director of transplant infectious diseases at the University of Pennsylvania in Philadelphia and chairperson of the ad hoc disease transmission advisory committee of the Organ Procurement and Transplantation Network.

She emphasized that the field has an excellent track record, citing the transmission of only two HIV infections from deceased donors and one from a living donor since 1987. "We're all trying to figure out how to make all of these things even safer," she said.