Transplant success and genes don't match up

When Ross Isaacs reviewed patient data on most of the nearly 900 unrelated living donor kidney transplants performed between 1988 and 1994 in the United States, he found large disparities in graft survival and patient survival among blacks, whites, and Hispanics, much as was found in studies of other transplant populations. But it is what this associate professor of medicine at the University of Virginia in Charlottesville didn't find that may have the most significant implications: conventional wisdom would suggest that genetic matching is very important in kidney transplantation, but in Isaac's data pool, traditional tissue typing methods such as HLA and even more contemporary matching by CREG did not predict rejection or graft survival.

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Cheryl Gerber Photography

Ross Isaacs

"We looked at a variety of variables, and we found the only two things that predicted graft survival were race and rejection, and rejection occurred independent of genetic matching," Isaacs said at the recent annual meeting of the American Society of Nephrology in New Orleans, Louisiana.

Unrelated kidney transplantation from living donors is growing in popularity, largely because of a dearth of available kidneys from living relatives and cadavers. Initial reports are that the procedure has excellent success rates, often despite significant HLA mismatching. Graft survival among living unrelated kidney recipients appears to be similar to survival among living related transplant recipients, and superior to survival among recipients of kidneys from cadavers.

But race seems to confound that success rate. Isaacs and his collaborators found that black recipients of living unrelated transplants had a 48 percent graft survival at four years, compared with 75 percent for whites and 88 percent for Hispanics. And more rejection episodes means fewer graft survivals for these patients, as was found in other populations.

In addition, survival data from this retrospective analysis leads Isaacs to assert that a patient who gets a kidney donation from a completely genetically mismatched living donor will do just as well, if not better, than a patient who gets a kidney from a perfectly matched cadaver. "This is raw data I've looked at," he said," there's no fudging."

But other experts in the field are not ready to discount the efficacy of tissue typing in picking the right kidney for a patient. Khalid M.H. Butt, director of transplants at Westchester County Medical Center, in Valhalla, New York, noted that past analyses have shown that fewer mismatched antigens increase the likelihood of graft survival, much more so than other factors.

However, people who receive perfectly matched genetic transplants still have rejections, and that suggests that there are other mechanisms at work in the process of graft host reaction, said Lawrence Agodoa, director of the End-Stage Renal Disease Program at the National Institute of Diabetes and Digestive and Kidney Diseases in Bethesda, Maryland. "Transplantation has been with us since the 1950s, and we very early homed in on this HLA system as being a very important predictor," Agodoa said. "But there are many other genetic factors here that may be at work that have influence on the HLA system, and vice versa, that we have not yet uncovered."

Stephen Brennan, assistant professor at Baylor College of Medicine in Houston, finds the conclusions of Isaacs' report compelling, especially because genetic matching does not always equal transplant success. "It is well accepted that tissue matching does impact survival, but the effect is more dramatic in other countries, including Japan," he says. "That may have to do with the heterogeneity of this country. There may be many different things we are calling [HLA antigens] that are in fact different molecules with a different immunologic effect."

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Alternatives to CFCs for medical uses

The importance of maintaining the ozone layer was emphasized recently at meetings of the American Association of Pharmaceutical Scientists in Seattle, Washington, and the International Conference on Ozone Protection Technologies in Washington, DC. During both meetings, executives from 3M Pharmaceuticals' (St. Paul, MN) drug-delivery program, along with representatives from the American Lung Association, the US Food and Drug Administration (FDA), and the US Environmental Protection Agency (EPA), discussed plans to protect the ozone layer by limiting the medical use of chlorofluorocarbons (CFCs), switching instead to non-CFC-based products.

The EPA's Nina Bonnelycke says that in 1994 alone "six million pounds of CFCs were released from metered dose inhalers (MDIs) made in the United States. Compared with the 40 million pounds of CFCs released from the servicing of automobile air-conditioning systems, this level of CFCs from MDIs is not insignificant."

The aggressive removal of CFCs from industrial and medical uses has spurred vigorous research and development of alternative compounds. One such compound is the hydrofluoroalkane propellant HFA-134a, which was approved in Europe in 1994 and in the USA earlier this year. This non-CFC compound has been successfully used in metered dose inhalers (MDIs). Proventil HFA, the first available CFC-free MDI, contains the asthma drug albuterol in suspension with the HFA-134a propellant.

Since 1974, CFCs have been known to be responsible for the breakdown of the ozone molecule, thereby depleting the atmospheric ozone layer. In the early 1980s, concerns over the environmental impact of CFCs resulted in the convening of the international Vienna Convention to Protect the Ozone Layer. This convention, sponsored by the United Nations Environmental Program, resulted in the writing of the Montreal Protocol on Substances that Deplete the Ozone Layer. Currently signed by over 150 countries, it took effect 1 January 1989.

After the Montreal Protocol was codified into US law in 1990, a complete ban on the production and importation of CFCs became effective on 1 January 1996. In addition, the year 2005 has been suggested as a target date after which CFCs will be banned from any "essential" medical uses as well. However, according to Tunde Otulana, medical officer in the Division of Pulmonary Drug Products at the FDA, the precise time for this final ban is still under discussion. "All MDIs used in the USA rely on CFCs as the propellant, and this propellant makes up 99% of the chemical formulation in the MDI," says Otulana, emphasizing the enormous impact these changes will ultimately have on the roughly 30 million MDI users in the USA alone.

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