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Researchers link organ transplant drug to rise in rare lymphoma

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A study led by Johns Hopkins researchers has linked the immunosuppressive drug mycophenolate mofetil (MMF) to an increased risk of central nervous system (CNS) lymphoma in solid organ transplant patients. But the same study also found that another class of immunosuppressive drugs, called calcineurin inhibitors (CNIs), given alone or in combination with MMF, appears to protect transplant patients against this rare form of lymphoma.

MMF and CNIs are given to transplant patients to lower the body's natural immunity and to prevent the new organ from being rejected.

"MMF remains one of the best current medications for immunosuppression that we have," says Amy Duffield, M.D., Ph.D., assistant professor of pathology and oncology at the Johns Hopkins University School of Medicine and a member of the Johns Hopkins Kimmel Cancer Center, "but a better understanding of its association with CNS lymphoproliferative disease will be crucial to further improving patients' transplant regimes based on all of the risks these patients face."

Blood cancers, such as lymphomas and leukemias, can be complications of solid organ transplants, but these cancers rarely start in the central nervous system, explains Genevieve Crane, M.D., Ph.D., a fellow in hematopathology at The Johns Hopkins Hospital.

However, in recent years, clinicians have begun to notice a rise in these

primary central nervous system (PCNS) lymphoproliferative disorders in transplant patients, according to Crane. The new study, described Sept. 16 in the journal *Oncotarget*, is believed to be the first large enough to identify a link between MMF treatment and these PCNS tumors, Crane says.

As part of the new study, Crane and her colleagues identified 177 cases of post-transplant lymphoproliferative disorder among patients seen between 1986 and 2014 at The Johns Hopkins Hospital. In that group, 29 people—mostly kidney transplant patients—were diagnosed with PCNS disease.

Crane says her team's analysis show no post-transplant PCNS cases diagnosed between 1986 and 1997, but the diagnosis increased markedly in the next decades. The proportion of post-transplant PCNS cases compared to other post-transplant lymphoproliferative diseases was fourfold higher between 2005 and 2014 compared to the proportion in 1995 to 2004, while the total number of post-transplant cases remained stable.

The researchers had prescription records on 16 patients who developed PCNS lymphoproliferative disease. Fifteen of them had been taking MMF in the year prior to, or at the time of, their lymphoproliferative disease diagnosis, while only 37 of 102 patients who had lymphoma outside the central nervous system had taken MMF.

However, the scientists also say they found that patients who took CNIs either alone or in combination with MMF seemed to be protected from developing PCNS disease. Among patients with a post-transplant disease, PCNS disease accounted for 66.7 percent of the cases among the six patients who took MMF but not a CNI, 23.9 percent of the cases among the 46 patients who took both an MMF, and a CNI; and only 1.7 percent of the cases in the 60 people who took just a CNI.

Crane worked with colleagues that included specialists in the Johns Hopkins University School of Medicine's Department of Pathology, blood and bone marrow cancer experts from the Kimmel Cancer Center, statistics and data analysis experts from the Johns Hopkins Bloomberg School of Public Health, a pharmacology expert from the University of Maryland, and a nephrologist from the University of California, San Diego. They found that these trends were largely the same in a set of 6,966 patients with post-transplant lymphoproliferative disease. Those patients' records were gleaned from an organ transplant database managed by the Organ Procurement and Transplantation Network and the United Network for Organ Sharing.

MMF was introduced for organ transplant patients in 1995. "Most solid organ transplant patients now receive MMF as part of their initial regimen," Crane explains. "There is a standard daily dose, and it does not require monitoring of drug levels in the blood. This is one of the major advantages of MMF."

CNIs, such as cyclosporine and tacrolimus, are also widely used in transplant patients, but they require careful monitoring to make sure that patients don't get a dose that would be toxic to the kidneys, Crane says.

Nearly 30,000 people receive solid organ transplants each year in the U.S. Some 1 to 2 percent develop lymphoproliferative disease of any kind, and 10 to 15 percent of that group develop the CNS type, according to Crane.

The monthly cost for an MMF ranges from approximately $67 to $90, depending on the dose, according to the Johns Hopkins researchers. CNIs tend to be more expensive, they say, ranging from $126 to $578 per month, depending on the dose and type of drug. CNIs also require periodic blood tests to monitor levels of the drug.

"More research needs to be done to confirm our results, but our work suggests that, at least in some patients, the combination of MMF and CNIs may be protective against CNS lymphoproliferative disease in a way that had not previously been appreciated," says Crane.

More information: Genevieve M. Crane et al. Primary CNS lymphoproliferative disease, mycophenolate and calcineurin inhibitor usage, *Oncotarget* (2014). DOI: 10.18632/oncotarget.5292

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