Radioimmunotherapy and Latent HIV Infection

In a December 3 presentation at the annual meeting of the Radiological Society of North America (RSNA) in Chicago, IL, investigators from Albert Einstein College of Medicine (Bronx, NY) reported on success in using a radioimmunotherapy (RIT) strategy to destroy remaining human immunodeficiency virus (HIV)–infected cells in blood samples of patients treated with antiretroviral therapy. News of the study results was reported by media worldwide. Although highly active antiretroviral therapy (HAART) has transformed the prognosis for patients infected with HIV by suppressing viral replication, this therapy is believed to leave reservoirs of latently infected cells. "In an HIV patient on HAART, drugs suppress viral replication, which means they keep the number of viral particles in a patient's bloodstream very low. However, HAART cannot kill the HIV-infected cells," said the study's lead author, Ekaterina Dadachova, PhD, a professor of radiology, microbiology, and immunology at Albert Einstein and lead author of the study. "Any strategy for curing HIV infection must include a method to eliminate viral-infected cells. In RIT, the antibodies bind to the infected cells and kill them by radiation. When HAART and RIT are used together, they kill the virus and the infected cells, respectively."

The research reported at the RSNA meeting builds on previous work by Dadachova and an interdisciplinary team of investigators. In 2006, with colleague Arthur Casadevall, MD, PhD, she described initial in vitro and animal studies of infection treatment with radiolabeled antibodies (*Q J Nucl Med Mol Imaging.* 2006; 50:193–204). In this study, the authors noted that: "The promise of this technique is based on the fact that the technology is largely in place and that the only requirements are availability of microbe-specific monoclonal antibodies and suitable radionuclides. In fact, one could anticipate that targeting microbes will be easier than targeting neoplastic cells when the enormous antigenic differences between host and microbes are taken into consideration." In the same year and with other Einstein colleagues, Dadachova and Casadevall published a report on selective killing of chronically HIV-1–infected human T cells in vitro and in mice harboring HIV-1–infected human peripheral blood mononuclear cells using radiolabeled (^{213}Bi or ^{188}Re) antibodies targeted at viral proteins (*PLoS Med.* 2006;3:e427). In 2012 the group reported on preclinical evaluation of a ^{213}Bi-labeled human monoclonal antibody (mAb) to HIV-1 gp41 glycoprotein in HIV-1 mouse models (*PLoS One.* 2013;7:e31866). They noted that their novel radiolabeled mAb reagent "could potentially be part of an HIV eradication strategy that is ready for translation into the clinic as the next step in its development." They added that the use of viral antigens promised "high selectivity, increased efficacy, and low toxicity, especially in comparison to immunotoxins."

In the study reported at RSNA, Dadachova and her coauthors Alicia McFarren, MD, and Dina Tsukrov, MS, administered the ^{213}Bi-labeled mAb 2556 to blood samples from 15 patients with HIV treated with HAART at the AIDS Center at Montefiore, the university hospital and academic medical center for Einstein. mAb 2556 targets a protein expressed on the surface of HIV-infected cells. The researchers found that this RIT strategy was able to kill HIV-infected lymphocytes previously treated with HAART, reducing HIV infection in the blood samples to undetectable levels. "The elimination of HIV-infected cells with RIT was profound and specific," Dadachova said. "The radionuclide we used delivered radiation only to HIV-infected cells without damaging nearby cells." The study also assessed the ability of the radiolabeled antibody to reach HIV-infected cells in the brain and central nervous system. Using an in vitro human blood–brain barrier (BBB) model, the researchers demonstrated that radiolabeled mAb2556 could cross the BBB and kill HIV-infected cells without overt damage to the barrier itself. "Antiretroviral treatment only partially penetrates the BBB, which means that even if a patient is free of HIV systemically, the virus is still able to rage on in the brain, causing cognitive disorders and mental decline," said Dadachova. "Our study showed that RIT is able to kill HIV-infected cells both systemically and within the central nervous system." The researchers are currently looking toward implementation of these findings in the clinical trial setting.

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