Race-based heart drug might stall search for better markers

The landmark approval of BiDil, a drug touted to treat heart failure specifically in blacks, has raised questions about the role of race-specific drugs in medical practice. Hearing early reports that the drug is already being prescribed to people outside the prescription guidelines, experts are calling for a biological marker that can better predict who will respond to the drug.

The US Food and Drug Administration (FDA) in June approved BiDil after studies showed that it improves mortality after heart failure by 43% among blacks; the drug was found to be ineffective in whites (*N. Engl. J. Med.* **351**, 2049–2057; 2004). It is not yet clear why the drug should be more effective in blacks, but one theory holds that BiDil compensates for a nitric oxide deficiency common in this population.

"Being black increases the likelihood of having that physiology, but it's no guarantee," says Jonathan Sackner-Bernstein, a member of the FDA advisory panel that recommended BiDil's approval. "Other people also respond nicely."

Geneticists and ethicists contend that race is a poor indicator of the underlying genetic or biochemical differences among different populations and could be a proxy for social factors (*Nat. Med.* **10**, 1266; 2004).

Sandy Huffaker/KRT

Color blind: The heart drug BiDil is prescribed specifically for blacks, but others are already clamoring for it.

Manuel Worcel, chief medical officer of Massachusetts-based NitroMed, Bidil's manufacturer, says the company is actively looking for genetic, biochemical or physiological markers that can predict who will respond to BiDil. "I believe this will expand the patient population," he says. Once the company identifies reliable markers, NitroMed aims to design a clinical trial that uses the biomarkers, rather than ethnicity, to select participants. Other researchers are meanwhile analyzing genetic data from a subset of participants in the original trial.

The FDA's prescription guidelines for BiDil are relatively broad, specifying the drug can be used for individuals with heart failure who identify themselves as black. But others are already asking their doctors about the drug—and some doctors are complying. "I would prescribe to non-African Americans who are already on standard therapy and not doing well," says Flora Sam, a cardiologist who led a segment of the BiDil trial at the Boston Medical Center. She says she has no financial arrangements with the company.

The drug's label allows for the broadest possible patient base, notes Sackner-Bernstein. "I don't think the product insert gives NitroMed major incentives to do further studies," he says. NitroMed set BiDil's price at $1.80 per pill, adding up to almost $10 per day, nearly double the cost of other heart-failure treatments.

BiDil is made up of two generic drugs, isosorbide dinitrate and hydralazine, an older blood pressure medication that has been associated with lupus, an autoimmune disorder three times more common among black women than white. Researchers conducting the BiDil trial did not routinely test for lupus, but report one case of the disorder among 518 trial participants. NitroMed officials say BiDil's hydralazine component is too small to be of concern, but more lupus cases may arise as the drug is used more frequently and for longer durations, says Sackner-Bernstein.

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Cholesterol drugs cut cancer risk, studies suggest

Drugs used to lower cholesterol levels may have unexpected benefits: some statins may also reduce the risk of breast and other cancers, according to evidence from six large epidemiological studies.

Statins cut the risk of breast, pancreatic, prostate and lung cancer by about 50%, scientists reported at cancer meetings in April and May. The studies together looked at more than 500,000 individuals.

Introduced in the 1980s to lower the level of LDL, or 'bad,' cholesterol, statins are the best-selling drugs in the US, with more than 11 million consumers spending more than $12.5 billion each year. But the cancer prevention aspect has come somewhat as a surprise.

"When the drugs were developed, there was some evidence that high doses caused liver cancer in rodents, so studies were done to determine whether they were carcinogenic," says Jim Dimitroulakos, senior scientist at the Centre for Cancer Therapeutics at the Ottawa Hospital Research Institute.

Instead, most evidence seems to indicate that the drugs reduce cancer risk. The most recent results build on previous epidemiological studies and show that people taking statins can cut their risk of pancreatic cancer by 59%, prostate cancer by 50% and colorectal cancer by 49% (*N. Engl. J. Med.* 352, 2182–2192; 2005). Some studies show that in comparison with other classes of cholesterol-lowering drugs, such as fibrins and bile acid–binding resins, statins may be superior in lowering cancer risk (*Arch. Int. Med.* 160, 2363–2368; 2000).

Evidence of statins' preventive power is mounting particularly with breast cancer. In a study of 2,000 women in Seattle, those taking statins for five years on average had a 30% lower risk of breast cancer (*Cancer* 100, 2308–2316; 2004). Lead investigator Denise Boudreau is conducting a prospective study of 84,000 women to examine the link between statins and cancers of the breast, prostate and reproductive organs over 14 years; results are expected in 2006. Data from analysis of statin use among 150,000 women in the Women's Health Initiative are expected later this year.

Statins' effect on cancer risk is plausible because the drugs inhibit many molecules necessary for crucial functions such as membrane integrity, cell signaling, protein synthesis and cell cycle progression, says Boudreau. For instance, cerivastatin has been shown to inhibit signaling pathways associated with metastasis in a breast cancer cell line and lovastatin inhibits mammary tumor formation and metastasis in mice (*Carcinogenesis* 22, 1139–1148; 2001; *Breast Cancer Res. Treat.* 50, 83–93; 1998). In cancer cells, statins have been shown to arrest growth, prevent invasion of distant sites, sensitize cells to the damaging effects of radiation and trigger cell death. Statins' effect might also be linked to cholesterol production in hormone-sensitive cancers, some researchers suggest.

If further studies confirm these results, the public health implications are significant. But randomized placebo-controlled studies must first clarify the exact nature of the effect, says Boudreau. "We also need to understand more about the risks associated with long-term use of statins."

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