Lipid-Altering Drugs: Decreasing Cardiovascular Disease at the Expense of Increasing Cancer?

To the Editor: The interesting paper by Cao et al. (1) exposes a disturbing paradox in preventive medicine that has significant implications. They demonstrated that expression of a mutant receptor for high-density lipoprotein (HDL) on breast cancer cell line MCF-7 inhibited the proliferation and attenuated the angiogenic effect of HDL on the breast cancer cells. This supports previous data suggesting that HDL is a growth stimulator for breast cancer cells (2), particularly estrogen receptor-positive cells (3). Raising HDL levels by lipid-altering drugs has been found to both prevent cardiovascular disease events (4–6) and decrease the angiographic progression of coronary artery disease (7–9). Therefore, therapeutically raising HDL may be a double-edged sword by decreasing cardiovascular disease at the expense of increasing breast cancer and possibly other malignancies. Recent literature suggests this may be true (10–13).

Several trials of cholesterol lowering with drugs to prevent cardiovascular disease events have demonstrated an increase in cancer incidents in the subjects treated with lipid-altering drugs (10–13). The trials were randomized, double-blinded, and lasted an average of 5 years. The lipid-altering drugs were statins or fibrates, and the HDL cholesterol levels of the subjects randomized to the drug were raised by 5% or more for the duration of the trial period. A statistically significant excess of malignancy was seen in elderly subjects (12, 13) and women (11) randomized to the drug groups. Alarmingly, breast cancer was diagnosed in 1 of 290 women in the placebo group and 12 of 286 women in the pravastatin group during a 5-year trial (P = 0.002; ref. 11). In another randomized study, involving elderly subjects with a mean age of 75 years at entry (13), the significant decrease in coronary death in subjects randomized to pravastatin equaled the significant increase in cancer death in the same subjects, leaving total mortality unchanged.

On balance, other trials of cholesterol lowering to prevent cardiovascular disease did not demonstrate an increase in cancer incidence or mortality (4–6, 14–16). However, these trials were severely underrepresented with women and the elderly.

Unfortunately, there is a paucity of long-term data using lipid-altering drugs for the prevention of cardiovascular disease in women and the elderly. It is possible that women and the elderly are susceptible to cancer-promoting effects of HDL raising. Meanwhile, there is a push to put more individuals on lipid-altering drugs, particularly women and the elderly (17). I feel there is a need for caution in the widespread use of lipid-altering drugs in women and the elderly, and they should be used when the risk of imminent cardiovascular disease is very great. More long-term data are needed and can be obtained by well-designed clinical trials. By pharmacologically raising HDL in certain segments of the population, we may be decreasing cardiovascular disease at the expense of increasing cancer.

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References


In Response: We reply to Dr. Mark R. Goldstein’s comments prompted by our recent report (1). Dr. Goldstein points to a statistically significant excess of malignancies in several trials involving the use of statins to lower cholesterol. Several large-scale statin trials have shown that lowering cholesterol rapidly reduces the risk of major vascular events not only in middle-aged patients but also in older patients. These studies have also shown that statin therapy is well tolerated and safe, even among older patients, without evidence of any increases in cancer or other nonvascular morbidities or mortalities (2).

In the PROSPER trial, patients randomized to pravastatin in PROSPER had a slightly higher diagnosis of cancer during the trial period. Much of the slight increase was observed early in the trial, soon after the start of therapy. In addition, there was no particular prevalence of cancer type, which suggests that it may have been due to chance. This conclusion is supported by the lack of any overall excess of cancer among patients of all ages randomized to pravastatin or other statins in the meta-analysis of previous large-scale trials as noted by investigators who participated in PROSPER. A nonsignificant trend toward more cancers among patients >65 years was also noted in another statin trial, but again no particular site of the cancer predominated (3).

Moreover, among more than 1,600 people with cancers recorded during Heart Protection Study, there was no significant excess among either young or old participants or at any particular site (4).
Incidence of breast cancer was 0.2% in the pravastatin-treated group and 0.1% in those assigned to placebo. An imbalance in breast cancer had previously been noted in the CARE (Cholesterol and Recurrent Events) study (5). The LIPID study, compared with CARE, enrolled a larger number of women. In the LIPID study, there were 10 reported cases (1.3%) of breast cancer in pravastatin-treated women and 8 reports (1.1%) of breast cancer in placebo-treated women. In addition, 2 cases of breast cancer were reported in men; both were in the placebo group (3).

Finally, Dr. Goldstein cautions clinicians regarding the widespread use of lipid-altering drugs in women and the elderly. Although our data show that high-density lipoprotein may contribute to the growth of breast cancer cells, these studies were done in vitro, and any attempt to extend these findings to clinical medicine is premature and unwarranted.

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Correlation between CXCR4 and Homing or Engraftment of Acute Myelogenous Leukemia

To the Editor: Tavor et al. (1) investigated the role of CXCR4 in the migration and development of human acute myelogenous leukemia (AML) stem cells in NOD/severe combined immunodeficient (SCID) mice. They reported that human AML cells home to the murine bone marrow (BM) and spleen in an SDF-1/CXCR4-dependent manner.

Recently, we investigated the correlation between the level of expression of CXCR4 on AML CD34+ cells and their ability to engraft the BM of NOD/SCID mice (2). We found the levels of CXCR4 expression on AML CD34+ cells to be decreased compared with normal progenitors. However, based on analysis of 11 AML cases with different CXCR4 levels, we found that engraftment of AML in NOD/SCID mice was independent of CXCR4. We demonstrated that not all AMLs engraft the murine BM, as described also by others (3–5). Cells with virtually absent CXCR4 expression were able to engraft, and cells from two patients with high expression of CXCR4 did not. Anti-CXCR4 antibody failed to block the engraftment of two AMLs into NOD/SCID mice.

Engraftment of AML in all cases in the study by Tavor et al. (1) could be partially explained by the use of NOD/SCIDB2mnull mice (4) or by the small number of patient samples tested for homing and for engraftment (n = 6).

Tavor et al. (1) demonstrated high expression of internal CXCR4 in all AML cases, even in the absence of external CXCR4. However, the correlation between cell external or internal CXCR4 and the ability to engraft is missing. It is also interesting to note that the number of homing cells was higher in patient 8 than in patient 11, despite the lower CXCR4 expression. In addition, in 7 of 21 cases studied, CXCR4 expression was not determined. It is not reported which AML samples were used for engraftment studies, what their CXCR4 expression was, and whether the remaining 15 AML samples engrafted.

With regard to homing (see Fig. 5 in ref. 1), the frequency of homing cells is reported in the range of 0.01%, i.e., 100 cells/10⁶. No background was reported for this assay, but Fig. 6 (see ref. 1) indicates a background of 0.1% to 0.2%. A frequency of 0.01% would therefore be well below the level of sensitivity of this assay. Furthermore, in Fig. 6C of ref. 1, the number of mice injected per sample is not indicated, nor is the actual percentage of leukemic cells found in the mouse BM. In the homing experiment, only one mouse per sample was analyzed.

In conclusion, we feel that the report by Tavor et al. (1) does not establish a correlation between CXCR4 and homing or engraftment of AML.

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treatment (10 μg of 12G5 monoclonal antibody coinjected with the human cells without washing of excess antibody to prevent expression and function of new receptors) significantly reduced homing. The background levels are either below the level of detection or in the range of 0% to 0.0001% in the murine BM and 0% to 0.0005% in the spleen as described previously with normal human progenitors (2). Setting background levels for homing assays is more stringent than engraftment analysis to exclude any false positive event that may affect the initial low frequency of homing cells. Engraftment, however, yields a much higher percentage of human cells within the murine BM, and therefore this analysis allows a higher and reasonable background of about 0.1% to 0.2%, due to nonspecific staining of murine cells that can be eliminated by less stringent settings of the gates. In Fig. 6C, three untreated mice and two mice treated with anti-CXCR4 for each of the four experiments were used to reveal the role of CXCR4 in AML repopulation. Moreover, results were represented as a percentage of the control due to the high variability in engraftment levels from different donors.

Monaco et al. (3) did not find a significant correlation between CXCR4 expression and engraftment levels by AML cells; however, a positive trend was observed. Rombouts et al. (4) revealed a correlation between CXCR4 expression by AML CD34+ progenitors and engraftment in NOD/SCID mice and that levels of CXCR4 are also a negative predictor of overall survival and relapse-free survival of patients. In our study, pretreatment of primary AML cells with neutralizing CXCR4 antibodies significantly blocked homing to the BM and spleen of transplanted mice in all six tested samples and prevented repopulation in cells from six other patients. Monaco et al. (3) pretreated AML cells from two patients before injection and did not observe inhibition of engraftment. Our studies did not include CXCR4 blocking before transplantation because blocking of homing will always lead to blocking of repopulation, as demonstrated with normal human progenitors. However, the different effect of anti-CXCR4 treatment is most probably due to washings of excess CXCR4 of the high dose used by Monaco et al. (3). Membrane expression of CXCR4 is dynamically regulated. We previously showed that CXCR4<sup>high</sup> sorted cells washed from excess Ab after sorting, display newly expressed receptors on their membrane, enabling partial recovery of receptor function and homing/repopulation potential (5). Newly expressed receptors will be neutralized by unwashed excess Abs, while washed cells can reexpress functional receptors during the long homing and repopulation processes but not during the short in vitro migration assay as shown by Monaco et al. (3). In addition, Plett et al. (6) showed that low concentrations of anti-CXCR4 can also activate and enhance engraftment of normal human progenitors, suggesting that anti-CXCR4 antibodies may act as agonist in certain conditions because the antibody binds the same site as the ligand SDF-1.

References

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