Editorial Comment

Finding Clues Through Meta-Analysis

In this issue, Nakaya and Goto publish a study in which they sought clues about the characteristics of patients who responded to fenofibrate therapy and those who developed adverse reactions. To do so, they performed what is sometimes derisively called *data dredging*, in which they reexamined studies they had performed and published in 1995. This exercise is often valuable in generating hypotheses. In my opinion, investigators should do more of this type of analysis—keeping in mind, of course, that these hypotheses may not be true. Investigators should only retest the most striking and important results derived from such reexaminations of their data on both good and poor responders.

For example, in the present work by Nakaya and Goto, the data indicated that patients with high triglyceride levels (≥ 150 mg/dL) had greater high-density lipoprotein cholesterol (HDL-C) levels while taking fenofibrate. Unfortunately, apolipoprotein A-I and A-II changes were the same in both groups, suggesting there was no biologic mechanism for this finding.

The authors generated a different but still interesting hypothesis: those whose baseline HDL-C levels were <40 mg/dL experienced greater increases in HDL-C than those whose levels were higher at the start of the study. No doubt, they should reexamine fenofibrate therapy with that hypothesis as the central question in another, separate study.

There is another area in which searching through meta-analysis data has a much stronger and better reputation. In examining adverse events (AEs), one can simply report what was found without resorting to any statistical manipulation or hypothesis generation. Thus, the ~25% of participants in these investigators' studies who experienced elevated aminotransferase levels merit further study. Many regulatory bodies understand that levels of alanine aminotransferase, aspartate aminotransferase, and creatine kinase are often elevated in carefully conducted clinical trials for various reasons. Occasionally, the patients simply have *transaminitis* (ie, a nonserious hepatic condition) reflected by elevated aminotransferase levels. In such cases, the aminotransferase levels frequently return toward normal as the trial continues. That may have been the case in the studies reported in this paper.

However, another cautionary flag was raised in the fenofibrate studies: the 1 patient who developed jaundice. Although establishing drug-induced liver disease in clinical trials remains an elusive goal, the conjunction of increased aminotransferase levels and jaundice may signal a type of hepatic damage. Another grouping of data, such as increased aminotransferase, bilirubin, and alkaline phosphatase levels, may indicate another type of drug-induced liver disease. Occasionally, one can establish the presence of liver disease by

examining the records of patients who left the study for any reason. If the investigators follow good clinical trial practice, they may detect early clinical signs of liver disease or enzyme abnormalities.

Some of the papers published in *Current Therapeutic Research*[®] reveal the benefits of carefully executed retrospective data analysis and meta-analyses, which both provide clues for important future hypotheses. Understanding patients who respond to a drug and those who develop AEs can be important pieces of knowledge for both the practitioner and the patient. Therefore, investigators must undertake such studies and handle their conclusions carefully.

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