This issue of Medicine & Health, Rhode Island is the perfect venue to discuss a new, potentially useful treatment for slowing progression of Parkinson’s disease (PD), because it is based on increasing uric acid levels, hence putting people at risk for gout and possibly cardiovascular disease. It forces us to focus on several important clinical issues, including iatrogenesis, and how does one, both practically and ethically, recruit for a study that may cause significant complications in return for which the subject is rewarded with a clap on the back and an enhanced feeling of altruism but nothing else?

The basic facts are straightforward. A few large studies of PD, performed for a variety of different reasons, have included, for safety purposes, uric acid levels. Analyses have shown, without conflict, that PD patients with higher uric acid levels progress more slowly than PD patients with lower levels. Studies comparing people with PD to those without PD have consistently shown that PD patients have lower uric acid levels. Uric acid is one of the body’s strongest antioxidants, and PD has been thought to result from excess oxidation within neurons. Thus elevated uric acid levels may be beneficial for people with PD. And although diet plays a role in uric acid levels, and diet may be altered in PD, experts believe that the differences in uric acid levels found in PD vs. controls cannot be explained by diet alone. These observations led to the idea of increasing uric acid serum levels to determine if this will slow PD progression. It must always be kept in mind that when one sees associations between potential cause and effect, that the connection, while robust, may not be what it seems. The connection between alcohol and lung cancer is strong, but is mediated via cigarettes, for example. Decreasing alcohol alone will not decrease lung cancer.

The first step required to study a new drug to determine if it will slow disease progression is to perform a safety study, to prove to the Food and Drug Administration (FDA), which regulates testing of experimental medications, that this drug is safe to test in PD. Of course, this requires testing the drug in PD patients, but the structure of the study is quite different for a safety study than it is for an efficacy trial, for the goal of the preliminary study is to demonstrate that the drug is safe, not that it is therapeutically effective. The rationale for this is that safety studies require far fewer subjects, and generally are much shorter in duration so that fewer people are put at risk should the drug ultimately be shown to be unsafe.

It is not easy to recruit for a study when the goal is safety, not efficacy. Most patients do not want a placebo; they want to feel better. Many of our efficacy studies promise the subjects that they will be able to take the experimental medicine once the placebo phase has ended on an open label basis. This is considered “fair” although it is an oddity of our testing system since the efficacy study is performed exactly to find out if the drug is, in fact, effective; so how, without knowing the results of the study, can we justify giving it to patients? In a safety study, we don’t even have any data, other than experimental, to indicate that the drug will be effective. In the case of a drug intended to slow disease progression, one doesn’t even feel better while taking the drug. Furthermore, in this particular study, we are even requiring a lumbar puncture to determine how well the study drug is altering urate levels within the cerebrospinal fluid, and, presumably, the brain.

Would I enroll in this study if given the chance? I like to think so. I’m not sure I should be running a trial that I wouldn’t participate in as a subject. My own reservations have to do with the long-term safety of the drug. Will the FDA allow a drug that may induce gout and all its complications to be prescribed for people with PD? Will people with PD be willing to take a drug that may cause gout? At the initial meeting of site investigators, I asked the group who had made the observations about urate levels and PD, and who had designed this trial, if any of them had ever had a kidney stone. No one in the room had besides myself. Having had a few I can vouch for each one being memorably painful. Would I take a medication that might precipitate such a thing? Maybe, if it really slowed PD down a lot. What about cardiovascular disease? I’ve got that too. How keen am I to further increase my risk?

Most patients don’t have a history of kidney stones, and if they did, they would not be urate stones, and the connection between cardiovascular disease and urate levels is no more solid than that between urate and PD.

So the final decision rests, as it should, on clinical equipoise. Should we, or shouldn’t we? We simply have insufficient data to make a decision. When this happens, and the stakes are high, it is time for a study to answer the question. Unfortunately for those in the early studies, safety comes first. The later subjects have the benefit of helping determine if the drug actually works.

If there were medals for altruism, those who volunteer for safety studies should get the gold ones. They truly reap no substantive gain.

– Joseph H. Friedman, MD

Disclosure of Financial Interests

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