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Drugs and trials: Lessons from Plato

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A report appears in the medical literature reporting a previously unrecognized side effect of a drug. It may be the unexpected appearance of a rare complication such as osteonecrosis of the jaw in patients who are treated with bisphosphonates (1). On other occasions, it is an increased frequency of a well recognized adverse event such as hyperkalemia in conjunction with the use of aldosterone antagonists (2). Usually, the assessment of risk occurs in medical journals. The new information is incorporated into practice and clinicians adjust their prescription of the drug based on their interpretation of the needs of each patient. However, more often than we care to admit, reports of an adverse event are accompanied by evidence of misconduct either by physicians prescribing the drug or the pharmaceutical company that manufactures the drug. Suddenly, the affair is prominently featured on the front pages of the New York Times and plays out in the public arena. The FDA weighs in, black box warnings are published, drug use is severely restricted or banned, legal proceedings are started and sanctions are imposed. Finally, the dust settles and physicians who are using the drug appropriately in clinical practice or in research trials look up and find that they can no longer prescribe an agent that they judge to be useful for their patients.

Rosiglitazone is a prominent example of a recent drug in which this sorry tale unfolded in the lay media and medical press. It followed shortly after the Vioxx® (rofecoxib) fiasco that came to light in 2004 (3). I have been involved with clinical trials of rosiglitazone as the principal investigator of an ongoing randomized clinical trial in patients with resistant focal segmental glomerulosclerosis (FSGS) that was getting underway at about the same time as the publication of a meta-analysis of the safety outcomes of trials of rosiglitazone in adults with type 2 diabetes mellitus (4).

The Novel Therapies for Resistant FSGS Trial (FONT) (DK70341) is designed to test antifibrotic therapies that may attenuate the progressive decline in renal function in patients with FSGS who are unresponsive to standard immunosuppressive medications. Based on preclinical data in animal models of chronic kidney disease (CKD), rosiglitazone was included as a test arm in the original study protocol. However, in March 2010, the FONT study design was modified and rosiglitazone was removed as an experimental intervention (5). This decision was reached because the widely publicized meta-analysis of the safety data indicated that rosiglitazone was associated with a two-fold increase in the rise of myocardial infarction and congestive heart failure (4). Based on these data, the FDA severely restricted the prescription of rosiglitazone and inserted a prominent black box warning in the description of the drug. As a consequence, the reputation of rosiglitazone was tarnished and enrollment into FONT ground to a complete halt because patients were afraid of being randomized to the thiazolidinedione arm. These concerns persisted even though the FDA was continuously monitoring the FONT trial and found no reason to suspend the study. Recently, the US Department of Justice reached a settlement in which Glaxo SmithKline agreed to plead guilty to three criminal counts of health care fraud, to settle civil charges

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brought under various federal statutes, and pay a \$3 billion fine in connection to actions surrounding false marketing of several drugs and including failure to report safety data related to rosiglitazone (6). There are many who question whether this penalty, the largest in US history, is large enough to redress the criminality surrounding the fraudulent marketing and reporting of adverse effects of rosiglitazone (6,7).

The status of rosiglitazone is now in the category of pariah drugs, comparable to thalidomide prior to its redemption for the use in patients with multiple myeloma. Is that a fair description of this thiazolidinedione? The question that confronts the medical community after the revelations of criminal misconduct in the testing of rosiglitazone is, Can there be any legitimate use of rosiglitazone in the wake of the FDA's actions? Searching for a way to frame this issue clearly, it may be useful to turn to ancient Greek philosophy.

In the Platonic dialogue, *Euthyphro*, Socrates seeks a universal definition of piety that can be applied to all human actions to determine whether or not they are pious. The argument proceeds in several stages but culminates in the following dilemma—Is the pious loved by the gods because it is pious? Or is it pious because it is loved by the gods? Expressing the medical problem in Platonic terms, is rosiglitazone deemed a bad drug by the FDA and the Department of Justice because it is bad? or Is it a bad drug because the FDA and the Department of Justice considers it a bad drug? If the first option is correct, then there is no justifiable place for rosiglitazone in the pharmacopeia for the treatment of any condition. However, if the later choice is right, then it is conceivable that the severe restrictions placed on the rosiglitazone may deny select patient cohorts, e.g., children and adults with refractory glomerular diseases such as FSGS, ethically justified access to the drug. Absent alternative treatments for their condition, these patients may lose an opportunity to benefit from the drug. To simplify the argument that follows, it is best to imagine the circumstance in which no closely related drug such as pioglitazone is available that might retain therapeutic benefit with a better safety profile.

It is important to state that the focus of this article is not on the variations in risk assessment in different disease settings or by different stakeholders in clinical care and research activity. Moreover, it is clear that drugs with similar levels of risk for serious complication may be viewed differently by the FDA and physicians even when they are used for treatment of the same disease. For example, in the context of the FONT study, patients were unwilling to accept the risk of rosiglitazone because of the unfavorable press surrounding the drug but would accept randomization to the adalimumab even though the risk of serious adverse events - cardiovascular events for rosiglitazone *versus* infection and malignancy for adalimumab - may be comparable for the two agents (8). However, rosiglitazone is now considered a fatally flawed drug because of the failure of GSK to report to the FDA all adverse events that occurred in the performance of clinical trials in type 2 diabetes. This enhanced risk of adverse cardiovascular events is genuine and has been validated in several meta-analyses. This even forced the premature termination of the TIDE study that was designed to verify the cardiovascular risks associated with rosiglitazone (9). In addition, I am not addressing the bioethical problem of whether the assessment of this cardiovascular risk is accurate and consistent by patients and physicians. The question I am raising is whether the characterization of rosiglitazone by the FDA is scientifically fair and should guide future use and testing of the drug in research studies.

The question of access to rosiglitazone in studies of glomerular disease such as FSGS is relevant because of the paucity of new drugs that are under development which show promise of efficacy based on preclinical investigation of glomerular diseases. Nephrology trails behind other medical subspecialties in the performance of randomized clinical trials for several reasons including the low incidence of serious clinical disease, the need for

collaborative multicenter consortia, and poor understanding of the prognosis of chronic kidney disease (10). However, another key contributing factor is the lack of feasible biological targets for the treatment and the small number of candidate drugs. Thus, it is important to fully evaluate all potential novel therapies in patients with refractory glomerular disease in an effort to preserve renal function in these patients. There is a great deal of preclinical evidence that rosiglitazone exerts a wide range of favorable actions in experimental models of chronic kidney disease, including reduction in fibrosis and decreased inflammation (11,12). This suggests that judicious use of thiazolidinediones could be beneficial in patients with resistant FSGS. One could advocate for a delay in testing until a safe and well tolerated thiazolidinedione is developed that maintains these favorable effects and minimizes off target adverse consequences. However, the pathways of drug development are unpredictable and prevalent patients require ongoing efforts to alleviate the severity of their disease. Control of disease is usually a slow incremental process and the cost of premature abandonment of rosiglitazone may be too high for current patients who have no other viable treatment options.

There is a pressing need for transparency in safety monitoring during the testing of new drugs and following approval of successful drugs to ensure that the assessment of the risk:benefit ratio is accurate and up-to-date. I fully support all efforts by the FDA and other regulatory agencies to encourage full and timely reporting of adverse events and to make this information available in a timely manner to patients and physicians who might use or be exposed to a drug. Moreover, the criminality of GSK's conduct during the studies of rosiglitazone in type 2 diabetes and its negligent failure to report adverse events are established unequivocally (3,6,13). There are profound difficulties in fostering open access to drug safety data in an environment where testing is conducted by large corporations driven by considerations of profit and loss. The police authority of the FDA is essential to ensure that the drugs that are marketed in the US and prescribed to patients are accurately labeled and fully characterized.

However, do the actions of the leadership of GSK, working in an environment in which drug testing is a business venture, reflect on the intrinsic qualities of the drugs that they promote, including rosiglitazone? I would suggest that corporations and corporate misconduct do not determine the intrinsic value of a drug. That is a determination that is made by pharmacologists, basic scientists, clinical researchers, and individual practitioners and they do their work best if they are given the opportunity to perform tests of any and all drugs that display properties that suggest potential benefit for patients. It is important that the vital actions of the FDA to prevent fraud and false claims not infringe the ability of physicians to exert their clinical judgment and discretion in providing drugs to their patient when they consider that the risk:benefit justifies use of a drug (7). Overzealous restrictions on the use of specific prescription drugs may create conflict with the other mission of the FDA, namely to foster patient well being.

One could raise the legitimate question that adopting my stance would permit drug companies to continue to manufacture and market drugs that have been the subject of criminal proceedings and enable them to generate profits that might undermine financial penalties imposed by a judicial settlement. This would suggest that sanctions for corporate misconduct should take precedence over patient well being and access to drugs that might be beneficial. One solution would be to enforce penalties directly on the perpetrators who were responsible for the misconduct rather than to impose financial fines that only affect the impersonal bottom line. Alternatively, companies could be required to supply drugs that have been tainted by their unlawful behavior for any clinical investigation that is deemed scientifically and clinically valid by an institutional review board and prohibited from making any profit from the sale of the drug base on new clinical indications.

Based on my experience with rosiglitazone, I suggest that there is an urgent need for enhanced surveillance of all stakeholders in clinical research to ensure that this important work is performed in accord with the most rigorous bioethical standards. Research scientists and clinicians must identify the most promising agents for testing base on high quality experimentation. Pharmaceutical companies must provide accurate information about drug safety. However, when the system fails, it is important that the reporting of malfeasance by physicians and pharmaceutical companies be balanced and highlights the nature of the specific problem in research conduct. The public should be made fully aware of the problem, the extent of risk of the drug, the generalizability of the hazard, and any residual benefit that might accrue to the drug for specific patients. Announcements of restrictions on drug use should be tempered by advice on the continuation of other research studies that are evaluating the drug for other indications and advice on continued use of the drug if the prescribing physician anticipates that the benefit will exceed the risk for an individual patient. This balanced reporting will enable the FDA to achieve its dual mission of policing drug production and testing and promotion of patient welfare. It will improve communication about drugs and help individual patients and physicians work together to make thoughtful decisions about continued testing and use of the drug. Complete withdrawal of a drug from the market would represent the only circumstance in which no further explanation about drug use would be warranted.

Returning the *Euthyphro*, at the end of dialogue, Socrates finally persuades Euthyphro to accept the conclusion that piety constitutes actions that are accepted as pious by the gods. In the world clinical research resting, I am concerned that this approach may result in denying select patients access to a drug may be beneficial to them. In clinical research, I would recommend a different conclusion than the one reached by Plato - drugs are worthwhile because they are intrinsically worthwhile. Even if the regulatory gods say that a drug is bad, the drug it may still be good enough to warrant continued evaluation and use in discrete circumstances in which the available information support benefit to an individual or group of patients (word count: 2271).

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