Reviewer's report

Title: Cyxlo-oxygenase-2 selective inhibitors and nonsteroidal anti-inflammatory drugs: balancing gastrointestinal and cardiovascular risk

Version: Date: 4 January 2007

Reviewer: Leslie Cleland

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General
Thank you for asking me to review the responses of Moore et al. to reviewers’ comments. My view of their paper is essentially unchanged. It is provides a summary of clinical trials data ostensibly with the view to weighing risks associated with COX-2 inhibition. The paper makes insufficient to effort to examine confounders (e.g. co-administration of aspirin), corruption of the literature (e.g. major publications of the VIGOR and CLASS studies), selection biases (recruitment of low CV risk patients) and so on. In spite of their claims of independence, the paper reads like yet another industry sponsored analysis with (surprise, surprise) sponsor’s Pfizer’s celecoxib emerging as the least toxic agents. It is a paper destined to reinforce product marketing rather than to inform scientists and other readers meaningfuly regarding the relative merits of or need for NSAIDs. It is noted that the absurd proposition that the greater morbidity of CV events versus GI events is merely subjective persists. If the paper is to be published it could be argued that this be retained as a hint to readers not to take the paper too seriously (c.f. Bradbury’s early reference to mint flavoured items in Mensonge).

The argument raised against inclusion of discussion of fish oil as an NSAID alternative is revealing as it provides an example of the shifting quantifier (singular request transmuted into challengeable universal proposition). “Let’s face it, we could write a book on alternative to NSAIDs”. The authors were not asked to write book about alternatives, but to place their analysis within the context of the availability of an alternative for inhibiting COX and reducing arthritis symptoms using a natural product (i.e. fish oil in appropriate doses) for which there is a robust literature regarding mechanism (inhibition of COX-1 and COX-2), presence of precisely defined inhibitory molecules (EPA, DHA & n-3 DPA), desirable anti-inflammatory effects not shared by NSAIDs (inhibition of IL-1 and TNF), reduction in cardiovascular risk by multiple mechanisms and reduction in cardiovascular mortality quantitatively similar to that achieved with statins. In addition, fish oil has been shown to be substantially NSAID sparing (~50% reduction in discretionary use) in multiple studies, to have good long term continuation rates and has not been associated with serious upper gastro-intestinal events. It is possible that the authors, along with many prescribers, have not been made aware of this information by their sponsor or other purveyors of pharmaceutical agents (from whom many prescribers receive most of their medical education, directly and indirectly). Thus, inclusion of reference to fish oil within the context of considering use of an NSAID would be helpful to doctors and patients as they weigh the risks, which ostensibly is what this paper is about.

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)
Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

Discretionary Revisions (which the author can choose to ignore)