Editorial

Is There Anything Else We Could Possibly Need to Know About COX-2 Selective Inhibitor Drugs?

The last 5 years have seen a considerable resurgence of interest in the pharmacotherapy of the rheumatic diseases led in part by the development and clinical availability of the COX-2 selective inhibitor drugs (COXIB). These compounds with their unique pharmacologic properties have been the subject of intense scrutiny given their reported preferential benefit/risk ratio and in particular their clinical efficacy, theoretically without the risk of GI toxicity when compared to alternative antiinflammatory compounds (NSAID). Although there are numerous publications concerning the COXIB in peer review journals, the 2 pivotal studies (CLASS and VIGOR) are the ones that have generated the greatest interest. Data from these studies have been analyzed, reanalyzed and subset analyzed with an intensity never before witnessed in the rheumatology literature. Regional, national, international and professional scientific meetings have devoted large amounts of time to the study and promotion of these compounds, complimented by programs sponsored directly by the pharmaceutical industry. Marketing activity has occurred with the great competitive intensity only seen previously in other therapeutic areas. Sales growth has exceeded even Sildenafil (Viagra).

Despite this exposure, at the 2002 American College of Rheumatology meeting in New Orleans, over 2% of the posters presented related to COXIB, a significant number on this one topic given the breadth and depth of potential rheumatologic subjects. Recent attempts to keep COXIB issues on the front page have included novel educational formats to maintain participants' interest although often lacking any new credible information. Even the issue of relative potential cardiovascular toxicity between the 2 currently available compounds seems to be losing momentum. Given the present state of knowledge and intensity of recent interest in the COXIB, the question arises: Is there anything else we possibly need to know about the COXIB, or have we reached a saturation point?

In an attempt to answer this question, 76 rheumatologists attending a national rheumatology meeting in Vancouver, Canada were asked to respond to their perceived need for more information on specific COXIB related issues. This exercise was undertaken to determine the learning needs of Canadian rheumatologists for the subsequent development of an accredited, interactive, educational program to be held at the Canadian Rheumatology Association meeting in 2003. Participants were asked to answer 21 previously unseen questions using a touch pad (audience response) system. Their possible response to each statement consisted of one of 5 options to a specific statement: I strongly agree; I agree; I need more information; I disagree; or I strongly disagree.

The questions were randomly distributed among an additional 27 questions on osteoporosis. Participants were given only 10 seconds to react to ensure spontaneous responses and discourage peer discussion. The data obtained were subsequently analyzed and the statements assigned to one of 2 groups. The first group consisted of those statements where respondents were largely concordant either resulting in the majority responding that they either agreed or disagreed with the statement. The second group consisted of those statements where there was discordance in the group between agreement and disagreement with the statement, or where there was a large number of respondents feeling that they needed more information (Table 1).

Among all the respondents, there was general concordance that they were comfortable with their level of knowledge of the mechanism of action of the COXIB, their analgesic and antiinflammatory benefit versus traditional NSAID, their efficacy in rheumatoid arthritis and particularly osteoarthritis when compared to traditional NSAID, and their therapeutic role in these 2 conditions. Participants were also in general agreement that they were comfortable with their ability to undertake risk stratification in making a decision on the choice of these drugs compared to alternatives and had a general comfort level in their safety compared to traditional NSAID.

These results are not entirely unexpected given that these topics have been the subject of many previous meetings and that the audience consisted of a group of highly experienced rheumatologists with firsthand clinical experience of the COXIB.

The second group of statements, where there was a lack of uniformity in response or where a high proportion of respondents felt that they needed more information, was somewhat more diverse. There was an overall lack of consensus as to whether toxicity and efficacy is directly related to the degree of COX-2 specificity exhibited by the 2 currently available or future compounds. The same was true for the relative efficacy of the 2 compounds when

Table 1. Concordant and discordant issues regarding COXIB among surveyed Canadian Rheumatologists.

CONCORDANCE	DISCORDANCE
Mode of action of COXIB	The degree of COX-2 specificity vs toxicity and efficacy
Analgesic/antiinflammatory benefits vs traditional NSAID	Head to head comparison of COXIB with respect to efficacy and safety
Efficacy in RA and OA vs traditional NSAID	Overall cardiovascular and renal safety of COXIB
Therapeutic role of COXIB in OA and RA	Pharmacoeconomic benefits of COXIB vs NSAID
Patient risk stratification; safety vs traditional NSAID	Safety/efficacy of second generation COXIB

compared to each other. Lack of consensus was also seen in those statements that related to the relative GI and renal toxicity comparing different COXIB and whether these side effects were class or molecule specific. Respondents also expressed lack of consensus in their confidence in the use of these compounds in patients with cardiovascular and/or renal disease, and also in the elderly. The pharmacoeconomic value of COXIB over existing traditional antiinflammatory options was of general concern. Finally participants expressed a strong desire for more information as to whether second generation COXIB are likely to confer a superior risk/benefit ratio than those currently available.

This exercise and the results obtained constitute a form of needs assessment for further COXIB information.

It is clear from the results that there is still a need for additional information concerning the COXIB that, to date, has not been met by the numerous programs sponsored by professional and industry providers. Many issues relating to the clinical utilization of the COXIB appear to have been adequately addressed, at least to the satisfaction of the participating rheumatologists in our cohort. However, other practical issues concerning the COXIB obviously still need to be addressed, although it is unlikely that answers to these will be resolved by any additional reanalysis of existing data. The concept and theoretical value of the COXIB hypothesis has met with a certain level of acceptance among rheumatologists, but important questions still need to be answered. This appears to be particularly true with respect to the potential benefit and risk of COXIB in relation to the degree of COX-2 specificity, and begs the question as to whether the development of new compounds that are more highly COX-2 specific would confer greater benefit or preferential toxicity profile than the current compounds. In addition, the development of the second generation COXIB is likely to raise the question in clinical practice as to their preferential profile over the existing COXIB, let alone the traditional NSAID. Despite the ongoing controversy on the relative cardiovascular and/or renal toxicity of the 2 existing COXIB, it is likely that concerns about these issues will not be allayed until the results of more focused studies addressing these specific questions become available.

Areas of potential interest in the future are likely to revolve around risk stratification, pharmacoeconomic benefit, and the use of newer compounds in subsets of patients including the elderly and those with cardio/renal comorbidities.

Is there anything else we could possibly need to know about the COXIB? Yes, but in the future our deliberations need to address the more specific, practical concerns that have been raised and not adequately addressed in previous educational programs. These must be resolved if we are to finally place COX-2 selective antiinflammatories in their appropriate therapeutic role. If the issue of the COX-2 specific antiinflammatories is not heady enough, COX-3 can only be just around the corner!

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