Yet another editorial about coxibs?

Only an eye-catching headline is likely to attract the attention of readers who have already pored over the “Vioxx affair” in the *New England Journal of Medicine*, *Biba*, the *Lancet* and even *le Chasseur Français* (the *French Hunter*). Everything has already been said: pharmaceutical companies withholding negative studies, corrupt and incompetent regulatory agency evaluators, naïve and reckless prescribers… But in the last few months substantial quantities of supplemental clinical data have appeared that now make it possible to analyze this controversy more dispassionately and draw lessons from it for the future.

**HISTORY**

Pharmacologically, we have long known that selective inhibitors of the cyclooxygenase-2 pathway (coxibs) have, like traditional NSAIDS, antiinflammatory activity, cutaneous and renal toxicity, and hypertensive effects. However, they have less gastrointestinal toxicity, and they modify platelet activity and therefore coagulation. It was not initially clearer whether this involved suppression of the NSAID anti-aggregation activity, or, even worse, prothrombotic activity. We learned from the Vigor study published in 2001 that rofecoxib significantly diminished the number of digestive complications (perforations, ulcer, bleeding) but increased the incidence of coronary events compared with the control arm receiving naproxen. More recently, placebo-controlled studies showed that rofecoxib and celecoxib increase the incidence of cardiovascular accidents during treatments that last at least 18 months, and the combination of parecoxib + valdecoxib has the same prothrombotic effect, within only 10 days of postsurgical treatment. So we all agree: these drugs induce an undeniable increase in cardiovascular risk, with an incidence that varies highly according to the studies but which may be on the order of one cardiovascular event per 100 patient-years.

**MORAL OF THE STORY**

Adapting an old saying about statistics, we note that “Therapeutics uses pharmacology as a drunk uses a lamppost: for support, not illumination”. Pharmacological data show that coxibs modify platelet function, but do not allow for any prejudgment as to whether this change increases the risk of thrombosis and cardiovascular events compared with placebo. Only controlled clinical trials now allow us to be certain of this risk. This increased risk for a secondary criterion of the Vigor study was suspected in 2000, but was only confirmed in recent months, as several studies all pointed in the same direction. Belated claims of early doubts are easy, but the absolute proof is only recent.

“Find a villain!” I am firmly convinced that the drug companies did not hide the information (although they did not put the most negative results at the top of the pile!). All the regulatory agencies – European, American, and French – legitimately approved these drugs for marketing several years ago, based on unquestionable efficacy data and correctly performed studies that showed a decrease in gastrointestinal risk. These assessors were neither reckless nor corrupt. From the beginning, they set restrictions and called for prudence about the cardiovascular risks. They have modified the recommendations for use as additional knowledge has become available. But the media, advertising executives, pharmaceutical representatives, and some opinion leaders, in trumpeting the therapeutic innovation of “coxibs”, succeeded in their goal of generating massive numbers of prescriptions.

“Extrapolation is not proof”. Before drugs are approved for marketing, they are only tested on several thousand patients. Real knowledge, especially of safety, is acquired only slowly, year after year. Unfortunately, the publicity about the reduction in gastrointestinal risk with coxibs caused physicians to write an extraordinary number of prescriptions for the elderly, who have both gastrointestinal but also cardiovascular risks. In this issue of *Presse Médicale*, Auleley *et al.* clearly show that coxibs in France were prescribed to patients who were older, more often diabetic, and with higher cardiovascular risk than patients in the randomized controlled studies. This very interesting and exhaustive
study, based on data from health insurance funds covering 2000 through 2003, demonstrates the danger of extrapolating study results to populations at higher risk. “To live happy, stay hidden”. Finally, if the early development of these drugs was limited to several hundred patients and optimistic pharmacological data about gastrointestinal toxicity, no one would have known about the cardiovascular risk until after many years of use, and still... Finally, only very large studies including thousands of patients over several years can simultaneously provide substantial quantities of data and generate new, sometimes unexpected discoveries. Let us rejoice that these studies have been performed.

**The Moral of the Moral**

“Slow and steady wins the race”. Outside of the rare treatment revolutions that justify an immediate change in prescription rules, it is often more prudent not to rush to embrace treatment innovations. In contrast to marketing claims and the rash rush to modernism, attentive critical reading of the results of randomized clinical trials often makes it possible to notice that a new drug is not necessarily of obvious benefit to the patient. It is thus better not to rush, to wait for confirmation of a favorable benefit/risk ratio and learn the true efficacy of a drug, especially among groups at risk, before deciding to change prescribing practices.

**References**

5 www.afssaps.sante.fr