Toxicology is an essential step in the drug discovery process. After lead candidate selection and optimization, the safety of potential drugs must be evaluated in vivo and in animal models. The case study at hand proposed several thought-provoking questions centered around toxicology—ranging from a broader discussion about the variation of toxicological requirements for different diseases to a more specific contextualization involving the VIGOR study performed on Merck's Vioxx drug. These will be explored further in the following discussion.

In Dr. Bracken's lecture on toxicology, the concept of a toxicologically perfect drug was explored. Several attributes were listed, but three stood out as "more important" than the others:

- Drug has high therapeutic index (>25 fold)
- Toxicity and side effects are non-lethal
- Mechanism of toxicity is well-characterized

A high therapeutic index is absolutely crucial when considering dosing. The therapeutic index is a ratio between the dose that yields a therapeutic effect, and that which yields a toxic effect (figure 1). An ideal therapeutic index is greater than 25 fold, so as to limit the risk of toxic effects when dosing is not precise. It essentially allows more variability in dosing which should make patients and healthcare professionals more comfortable using the medication.

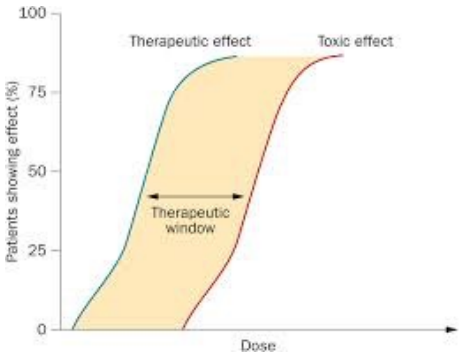

Fig. 1 Drug Therapeutic Window (Mathijssen)

When toxicity cannot be avoided or a high therapeutic index is not possible for a drug, it is desirable then for the drug to have non-lethal side effects. For obvious reasons this is safer to the patient; however, it begs the question as to which side effects and to what extent non-lethal side effects are acceptable. Non-lethal side effects may still decrease the health or quality of life of the patient. If side effects are not avoidable, it is best if they are reversible or treatable by simple mechanisms (e.g. dietary or lifestyle changes, or combination therapy).

An extension of having non-lethal side effects would be having side effects that are at least understood. A mechanism of toxicity that is well understood will be easily modeled in animals and humans, is not linked to the method of pharmacologic action, and will have minimal "secondary pharmacology" meaning its therapeutic profile is "clean" and precisely effective for the intended pharmacologic purpose. Knowledge on the mechanism of toxicity is crucial because it allows monitoring before, after, and especially during treatment with the drug. This idea goes hand in hand with identifying quantifiable, easy to monitor biomarkers.

These attributes are universally important; however, their hierarchy may differ depending on the approved indication. For this reason, it does not make medical sense to standardize toxicology requirements. Let us consider the case of statins used to treat high cholesterol and a cytotoxic chemotherapy drug to clarify this point. A patient taking simvastatin for hypercholesteremia will likely be taking the drug for a prolonged period, potentially a lifetime, and he is likely to be

middle aged or elderly and taking additional medications (Brinton). This is important because prolonged use will increase potential for exposure to adverse effects, and polypharmacy may cause drug-drug interactions. Prolonged use of statins have been linked to skeletal muscle toxicity and liver tumors, particularly in combination therapy (e.g. gemfibrozil) (Tobert) as well as increased risk for ductal and lobular breast cancer in older women (McDougall).

The mechanism of toxicity in skeletal muscle is widely acknowledged but poorly understood; however, other factors that put a patient at risk for this particular adverse effect are characterized, and biomarkers/monitoring strategies have been in place for several years (Brinton). This allows doctors and patients to evaluate risks and make informed decisions on medication choices. It also illustrates why all attributes of the "toxicologically perfect" drug are important and desirable- when one is unachievable, presence of the others may help offset the danger it poses to the patient.

This supports the point that toxicology should not be standardized. Additionally, considering the other scenario proposed earlier, a cancer patient undergoing chemotherapy, the requirements should be much different. This patient is likely more concerned about efficacy and survival than long-term side effects and likely to try a first-in-class drug or drug with less than optimal pharmacology and toxicology because it could be his best or only option. This could be said in general for terminal diseases. It may be acceptable to have reproductive toxicity in someone with stage four cancer, for example, while this might not make sense for someone in their thirties taking a statin medication.

Without standardized toxicology requirements, it becomes of the utmost importance that healthcare providers are well-informed of the risks and benefits of drugs so that decisions will be calculated and informed. A very well-known example of weighing risks and benefits in the pharmaceutical world is Merck's VIGOR study, VIGOR being an acronym for Vioxx Gastrointestinal Outcomes Research Trial.

The VIGOR study was organized to evaluate the COX-2 selectivity of rofecoxib (Vioxx) in comparison to a non-selective COX inhibitor (NSAID), Naproxen. It was a double-blind, randomized study of more than 8,000 rheumatoid arthritis cases looking specifically at clinically significant gastrointestinal (GI) events over a period of nine months (Bombardier). Towards the end of the study, the safety and monitoring board overseeing potential patient safety concerns proposed the idea of developing a plan for data analysis involving serious cardiovascular events. Merck accepted the idea and set cutoff dates for reporting adverse cardiovascular events (Bombardier).

The Bombardier et al. paper in the New England Journal of Medicine defends the VIGOR study on the basis of three disputed points that it attempts to puts to rest with evidence. The first criticism was that three myocardial infarctions were not reported in the published VIGOR study. The authors reveal that the dates these events were reported were outside of the allotted timeline provided by the data analysis plan for cardiovascular events Merck developed. In the second

point, the authors extend the justification for excluding these events by showing that the increase in overall relative risk of Rofecoxib from 4.25 to 5 was not statistically significant. The last point of contention involves the removal of a table from the original VIGOR study, which Bombardier et al. explain were summarized in the text instead.

Though Bombardier et al. seem to shield some of the blame from Merck for their clinical trial conduct, several questions concerning Rofecoxib remain. Ultimately, the undisputed results of VIGOR included reduced GI events associated with Rofecoxib when compared to NSAIDs. The differences in cardiovascular events between the two drugs was hotly contended at the beginning of the new millenium.

In 2001, two scientists from Merck Research laboratories presented the VIGOR study at the FDA Arthritis Advisory Committee. At this time, it was believed that the difference in cardiovascular events were not an adverse effect of Rofecoxib, but the result of a protective effect of Naproxen. It was noted in previous studies that while a COX-2 selective inhibitor effectively inhibited lately aggregation via synthesis of prostacyclin, that a non-selective COX inhibitor, such as Naproxen, additionally inhibited the promotion of platelet aggregation by decreasing thromboxane synthesis (McAdam). This is summarized at the left in figure 2. It was concluded by both MD presenters at the Arthritis Advisory Committee that the clinical effects of Rofecoxib were thus due to its selective inhibition of COX-2 and the poorly understood yet noted "cardioprotective" properties of Naproxen (Goldmann).

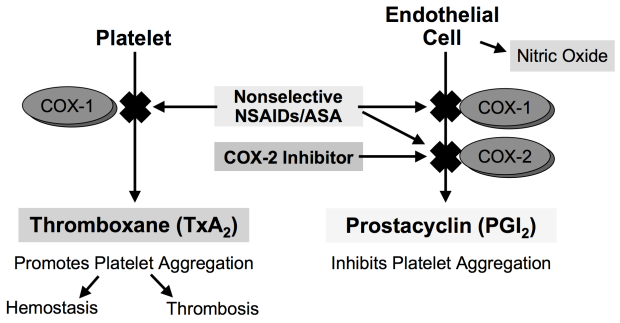

Fig. 2 Effects of NSAIDs on Thromboxane and Prostacyclin (Goldmann)

As noted, Drs Goldmann and Reicin who presented at the Arthritis Advisory Committee had Merck affiliations. This could have been a source of bias. Regardless, in 2007 a more comprehensive study of Rofecoxib's cardiac toxicity was performed by Mason et al. The authors propose two mechanisms for Vioxx toxicity:

- Rofecoxib increases susceptibility of human LDL and cell membrane lipids to oxidation. This is a hallmark feature in atherosclerosis (Mason).
- Rofecoxib's primary metabolism involving cytoplasmic reductase and its chemical structure cause it to form a reactive anhydride in the presence of oxygen that promote non-enzymatic formation of isoprostanes—molecules with an important role in the inflammatory mediation of atherosclerotic plaques (Mason).

These events were not observed with chemically distinct members of the same class of COX-2 selective inhibitors (e.g. sulfonamide) under identical conditions (Mason). This study and others (e.g. Davies) noted in the bibliography including meta-analyses and additional clinical trials

performed in the wake of Vioxx's removal from the market in 2004 serve to conclude that unique structural and chemical properties of Rofecoxib are responsible for its cardiac toxicity.

A question that is still unanswered is that of a second chance for Vioxx. I do not believe the evidence points to this being a reasonable direction of scientific inquiry and this opinion is based on my earlier discussion of the three most important toxicological attributes of a drug. At the time Vioxx was introduced to the market, selective COX-2 inhibitors were a new class of drugs providing a promising avenue of therapy for those suffering conditions involving chronic pain.

Much like that statin drugs, then, Rofecoxib therapy was never intended to be a temporary fix for these patients. In those specific cases (e.g. rheumatoid arthritis), if Vioxx was reintroduced, consistent use and risk of cardiac toxicity would need to be weighed against the benefit of pain management free of adverse GI events. As Vioxx was an early selective COX-2 inhibitor, the high relative risk for adverse cardiac events might have been acceptable; however, there are many more COX-2 inhibitors available now that do not pose the same cardiovascular risks. For this reason alone it does not make logistical sense to expend effort on Vioxx.

Again reiterating Dr. Bracken's points, now that the mechanism of toxicity for Vioxx is better understood, one could propose that it could be altered chemically and then make a case for further development including clear biomarkers. If this were to occur, it would remain essential for doctors and healthcare providers to be informed of the inherent toxicity and to stick to the advised indication. In class, the question was posed as to whether Vioxx should be indicated for headaches. This opens up an entirely different discussion, but relates to this case study in terms of ideal toxicology. If Vioxx had a better toxicological profile, perhaps we, as rising members of the healthcare industry, might not need to concern ourselves with off-label use.

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