

Questions to Dr. Temple

JOINT MEETING OF THE ARTHRITIS ADVISORY COMMITTEE AND THE DRUG SAFETY AND RISK MANAGEMENT ADVISORY COMMITTEE

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Highlights

- **“REFERENCE STANDARD” AN ALTERNATIVE TO ALLHAT:** Dr. Nissen said that it would be difficult to do Dr. Temple’s proposed ALLHAT-type study, and suggested as an alternative having an active agent “reference standard” to which all other drugs would be compared, and that naproxen would be the best candidate. Dr. Temple responded that he actually said the same thing at the bottom of one slide but that he would still like to know if naproxen is “less bad” or “really good”. The sponsors used different comparators in different trials so that, for example, one did not have a direct naproxen-ibuprofen comparison.
- **IF NAPROXEN+ PPI SAFE FOR GI, COX-2 SELECTIVE DRUGS ARE OF LESS VALUE:** Dr. Temple asked if naproxen alone or naproxen together with a PPI should be used as a comparator. His own feeling is that some more data on this question is needed, but if the PPI protects against naproxen’s GI adverse events it raises “the fundamental question of how much help you get from being COX-2-selective”.
- **NO DATA ON GI SAFETY OF ASPIRIN+PPI:** Dr. Cryer thought that use of “full-dose aspirin” (if this means 3.9 grams a day) would be “non-practical”. Dr. Temple asked what would happen if you added a PPI to aspirin, even short term using endoscopic ulcers as an endpoint. Dr. Cryer said “I don’t know and I don’t think that it will ever be known”.
- **COX-2+ASPIRIN = NSAID IN ENDOSCOPIC ULCERS, = NSAID+ASPIRIN IN GI EVENTS, AND LESS THAN NSAID+ASPIRIN IN GI HOSPITALIZATIONS:** Dr. Cryer commented on Dr. Temple’s suggestion of how a combination of celecoxib and 80 mg aspirin would look in terms of the GI effect. “With respect to endoscopic ulcer, COX-2 plus aspirin equals traditional NSAID”. With regard to hospitalizations, an unpublished Canadian study shows that with “COX-2 plus aspirin ... hospitalizations ... are less than hospitalizations for non-selective NSAIDs plus aspirin”. Abstracts of outcome studies indicate that GI events “on COX-2 plus aspirin are

similar to events on non-selective NSAID plus aspirin”.

- **IS THERE A (COX-2 + ASPIRIN) COMBINATION WITH CV SAFETY AND GI BENEFIT?** Dr. Temple suggested that it might be possible to combine some level of COX-2 selectivity (from one of several drugs with different degrees of COX-2 selectivity, or different doses of a COX-2 selective drug) with some dose of aspirin so as to mitigate the adverse cardiovascular effect while retaining some of the benefit of less GI safety problems. He conceded that “the data so far don't show that. But they didn't seem definitive to me”.
- **PROBABLY HIGH DROPOUT RATE IN 1-2 YEAR OA ALLHAT-TYPE TRIAL:** Dr. Cush said he liked the idea of an ALLHAT-type study but it would be hard to keep OA patients on the assigned treatment over a 1-2 year trial period. Drugs to be compared could range from highly selective COX-2 inhibitors to less COX-2 selective drugs, to non-selective NSAIDs to pure analgesic drugs.
- **“LARGE SIMPLE TRIAL” MAY BE PREFERABLE TO ALLHAT-TYPE DESIGN:** Dr. Hennekens expressed a preference for a “large simple trial” rather than an ALLHAT-type trial.
- **“COLLABORATIVE” ALLHAT-TYPE TRIAL WITH FDA, NIH & SPONSORS:** Dr. Abramson suggested that the ALLHAT-type study might be feasible if FDA, NIH and sponsors all contribute to “collaborative study” that includes biomarkers, pharmacogenomics, and blood pressure. Dr. Temple agreed but said that some of the drugs are

generic and unlikely to get sponsor support – “you noticed I didn't have a slide on how to do this”.

- **HIGH-DOSE ASPIRIN AND THROMBOSIS:** Dr. Ilowite mentioned a study in Kawasaki disease in which high-dose aspirin appeared prothrombotic, possibly because of prostacyclin inhibition at these high doses. Dr. Hennekens said that in 135 randomized trials in over 212,000 subjects, all aspirin doses between 75 mg/day and 2 grams/day had “significant cardiovascular benefits” and there is no cardiovascular “reversal of benefit” at high doses. Ongoing randomized trials are evaluating beneficial effects of high-dose aspirin on endothelial function, nitric oxide formation and other measures of anti-atherogenic effects.
- **FULL ANALGESIC DOSE OF ASPIRIN LESS THAN FULL ANTI-INFLAMMATORY DOSE:** Dr. Cush suggested that the aspirin dose might be selected to provide analgesic effect rather than anti-inflammatory effect.
- **“GATE” STUDY SHOWS NO INCREASED CV RISK WITH CELECOXIB 200 MG QD:** Dr. Cush mentioned that the completed GATE study is a 1,588-patient, 6-month, OA trial that is presently being analyzed. One of the 5 arms of the trial uses celecoxib 200 mg once daily and the DSMB has found no “increase in cardiovascular events including M.I., any difference between the Celebrex group and the other four control groups”.

Presentation Text

DR. WOOD: We will take a few minutes, a very few minutes, for questions to the last two speakers and then we will take a break and be back. So the panel needs to remember that they are eating into their break. Dr. Nissen?

DR. NISSEN: Quickly, Bob, Bob Temple. The difficulty, of course, in the ALLHAT study is that it is very--it seems unlikely that it will get done. So the question is, putting some constraints on this, and I thought about this last night in some detail into the wee hours of the morning, it seems to me that what we really need for this class of drugs is a reference standard. That reference standard, unlike many studies, can't be placebo because you can't treat arthritis patients with placebo. So I would submit to you that, if you are going to do comparisons, that the reference standard, the best reference standard we have, is naproxen because we know as much about it as anything else. We think it is, at worst, neutral and maybe a little better than neutral. So I would argue that, if you want to do ALLHAT light, then what you do is you test every agent both that stay on the market and that are proposed to bring onto the market against naproxen with an adequately sized trial and you set an upper bound, which we have to talk about, about what the upper bound of hazard you are willing to accept is, and the test that you run is on efficacy and on cardiovascular hazard. If your drug is beaten by naproxen, you don't make it. If you can

show equivalence within a reasonable upper bound of naproxen, then we would be pretty comfortable--I think I would be pretty comfortable that the drug is not going to create a hazard. What do you think about that strategy?

DR. TEMPLE: That is actually--I went through it very fast, but that is actually what I said at the bottom of one slide. I still would like to know better whether the naproxen is less bad or is really good. Therefore, as I said on the slide, in my heart, I would like to see somebody try to give full-dose aspirin for a while because we are really pretty sure that won't be bad. I think the community, in the long run, needs that. Who is going to do it? That is a perfectly good question. I do want to point out, though, that the way some of the trials were done, like TARGET, they could have given answers on some of this, or at least closer. But, because they did separate trials, instead of randomizing to each of the treatments, that was obscured. You could have had a very substantial naproxen-ibuprofen comparison, but you didn't get it because of the structure of the trials. So I think it is very important to randomize to each of the treatments, obviously, whatever it is. But that would be my best guess at the moment. But, in line with what Alastair asked before, when you do naproxen and you are looking at G.I. effects, do you add a proton pump inhibitor? I think you need a little more information before you do that, but you might say that, which then raises the fundamental question of how

much help you get from being COX-2-selective.

DR. WOOD: Dr. Cryer?

DR. CRYER: I wanted to comment on several of the questions, Dr. Temple, that you raised as well to ask a question. I guess I will just ask the question first. When you say "full-dose aspirin," are you referring to full anti-inflammatory doses of aspirin, 3.9 grams a day or--okay.

DR. TEMPLE: Which I assume most people will not tolerate and there will be huge bleeding. So you have got to do something.

DR. CRYER: Right. See, I think that is a non-practical experiment design and I think we have come a long way from 3.9 grams of aspirin per day, particularly because of the concerns of the adverse events, the salicyism, the G.I. events. Clearly, 100 percent of those people are going to have gastric ulcerations assessed endoscopically. So I also would prefer one of the newer NSAIDs, traditional NSAIDs, in that comparison. With regard to--

DR. TEMPLE: Actually, before you leave that, do you know what would happen if you added a proton pump inhibitor to aspirin?

DR. CRYER: Not at 3.9 grams a day. I don't think anybody thought that would be a feasible design.

DR. TEMPLE: Short term, then, just to look at endoscopic ulcers.

DR. CRYER: I don't know and I don't think that it will ever be known.

DR. TEMPLE: Then I won't get the answer.

DR. CRYER: What I do know is that, if you give 3.9 grams of aspirin per day in the short-term, greater than 90 percent of your patients who take aspirin will have endoscopic ulceration. I don't know what the effect of the PPI would be. I wanted to address your last kind of question that you threw out there of whether or not a short-term study would show that celecoxib plus 80 milligrams of aspirin would have a favorable effect, a G.I. effect, compared to a non-selective NSAID. Those experiments have been done. With respect to endoscopic ulcer, COX-2 plus aspirin equals traditional NSAID. With regard to hospitalizations, having said that, there is a recent study not yet published, epidemiologic study from Canada, indicating that COX-2 plus aspirin, hospitalizations for that are less than hospitalizations for non-selective NSAIDs plus aspirin. Then we have outcome studies, not yet fully published, in abstract form which indicate that events on COX-2 plus aspirin are similar to events on non-selective NSAID plus aspirin--G.I. events.

DR. TEMPLE: It is possible that if you add aspirin--I mean, it is sort what I would expect--is that you would get something that is a lot closer to being--in a cardiovascular sense, a lot closer to being just a regular NSAID and maybe you would still have some residual advantage in a G.I. sense. But, I must say, the data so far don't show that. But they didn't seem definitive to me. It raises the question of--you know, the idea of COX-2 selectivity is, at least, in part, a conceptual and promotional idea.

As Garret pointed out the first day, five or six of those old drugs that aren't coxibs are COX-2-selective. So there is a whole range. My feeling is we need to understand the consequences of what all that means and there is a somewhat artificial separation between the coxibs and the others because those old drugs at least are partially selective and may have some of the same properties. So one of my hopes that we could look at a range of these.

DR. CRYER: With respect to your last comment, I am entirely in agreement with that.

DR. WOOD: Let's move on. Dr. Cush?

DR. CUSH: ALLHAT, I like the intention of it. I would suggest, though, that if you are going to have a study long enough to pick up some of these events, a year or two, it is going to be very, very hard to keep O.A. patients on one of those drugs. So maybe actually stratifying according to pure COX-2-specific drugs to COX-2-selective drugs to the non-selective drugs that are more predominantly COX-1 and then having a totally nonsteroidal, non-nonsteroidal group, which would be the Tylenol group you talked to or other analgesic agents might work over the long term.

DR. TEMPLE: That would answer a lot of the questions. My real hope--you have a better idea whether it is possible than I do--is that you could actually find a population that could be given what we are pretty sure is a cardiovascular-neutral treatment. That is really the only way to pin this down and it does seem worth pinning down.

DR. WOOD: Dr. Hennekens?

DR. HENNEKENS: I think I gleaned from Dr. O'Neill that if we determine there is a class effect that it varies not just by drug and dose but by duration of therapy. From Dr. Temple, the comment that--I am very attracted to the concept of what I would call a large simple trial rather than an ALLHAT trial. I think there is merit in seeing aspirin studied in therapeutic doses and I think there is evidence that anti-inflammatory effects are seen at doses far lower than the 3.9 grams. But the question I have for Bob is there are three currently marketed FDA-approved coxibs. So would you include valdecoxib and 25 milligrams of rofecoxib in your design?

DR. TEMPLE: Part of the reason I didn't address that is I figured that is what the committee is going to talk about. I was willing to say that the celecoxib data look funny enough so that you might consider it.

DR. WOOD: That is part of what we are going to discuss.

DR. TEMPLE: That is what you are going to discuss so I didn't address it.

DR. WOOD: Let's move that to later. Dr. Domanski?

DR. DOMANSKI: I will pass.

DR. WOOD: Dr. Abramson?

DR. ABRAMSON: Thank you. I want to probably say something rather naive in support of the study, Bob, and that is that we are at a moment where we can do a paradigm shift, meaning that study that you propose is an important one but it is very large and it is going to be very hard

to get any resources to do that. I think we are at a moment where for the companies and the FDA and the government to think about a collaborative study where, if you have a drug that has some--this information is important, that we put together a collaboration among industry to do a multi-arm study of multiple drugs. It is something, you know, in the osteoarthritis field, the companies have supported largely this osteoarthritis initiative through the NIH to look at outcomes in large numbers of patients. I think what we need is a similar COX-2 initiative where either with the FDA or the NIH participating, with collaboration among industry, we are doing a multi-armed large study with biomarkers, with pharmacogenomics studies, with genetics and other blood pressure, but try and do it in a utopian way. I think everyone here wants to get the right answer, whether it is in industry or here at the table. This could be a good opportunity to do something very differently than we have done before in a large trial.

DR. TEMPLE: I don't disagree at all. I mean, some of the drugs are generic. They don't have any company that is massively interested in them. So it is going to be a mixture of government, generosity and a wide variety of other things that are scarce. So I don't know how to--you noticed I didn't have a slide on how to do this.

DR. WOOD: Dr. Ilowite?

DR. ILOWITE: Just a minor point. I understand the need for a cardiovascular-neutral anti-inflammatory drug in an ALLHAT study. But I was a little confused because I am aware of

some literature directed at people who are interested in Kawasaki disease suggesting that high-dose anti-inflammatory aspirin is actually prothrombotic because of differential effects on prostacyclin and thrombotics.

DR. TEMPLE: There are aspirin studies going back to at least moderate doses that show beneficial effects. It is not just 80 milligrams. It is certainly at least a gram a day. Some of the early ones were more than that. That is worth thinking about. I am encouraged by the thought that you might be able to get away with doses less than 3 grams. So I didn't know that it was considered prothrombotic. I thought aspirin always looked good. But that is not up to grams. I don't think any of the studies have done anything like that.

DR. WOOD: We will give Dr. Fleming the last word.

DR. FLEMING: I am just debating whether to do it now or after the break.

DR. WOOD: Let me help you. Go ahead.

DR. FLEMING: Now?

DR. WOOD: After the break will be great.

DR. FLEMING: All right. I will wait.

DR. WOOD: We will take a break and then we will be back here in ten minutes. (Break.)

DR. WOOD: Okay, folks. Let's get started. The next presentation will be given by Sharon Hertz who is Deputy Director of the Division.

DR. HERTZ: Thank you. I am just going to spend a very few minutes summarizing some of our--

DR. WOOD: Let me, in fact, just before Sharon begins--Sharon Hertz has passed out a handout that includes a lot of her slides. In the interest of time, she has graciously agreed to delete some of these slides and just focus on a smaller subset of what is in the handout. However, the committee does have the handout and the committee may find that handout useful for referring to some of the data.

DR. HENNEKENS: Alastair, a quick comment. I want to make a quick clarification on the earlier comment about pro-inflammatory effects of high doses of aspirin.

DR. WOOD: Sorry; I missed that. About what?

DR. HENNEKENS: In the randomized trials, 135 randomized trials with over 212,000 randomized subjects, whether the doses of aspirin are 75 milligrams or up to 2 grams a day, there are significant cardiovascular benefits to aspirin even at high doses. The issue, as Bob pointed out, at the high doses, is not that there is a reversal of the benefit but that the side effects are increased. So I think that is an important point to make.

DR. ILOWITE: I just wanted to say that in pediatrics, we think of anti-inflammatory doses as 100 milligrams per kilogram. So those are the doses I was speaking of.

DR. GIBOFSKY: Finally, the high-dose aspirin that would be necessary to treat patients with rheumatoid arthritis of 3.9

grams or greater would have significant problems on the stomach, as Dr. Cryer said, significant problems on the hearing of the patient and significant problems, perhaps, on other organ systems as well. It is not a study that could be easily undertaken.

DR. HENNEKENS: I won't debate the value of the study of 3.9 grams of aspirin but, from the perspective of anti-inflammatory effects, they have been observed at doses of 2 grams of aspirin a day and, in fact, there are randomized studies going on directly comparing that somewhat higher doses of maybe 1 to 1-and-a-half grams a day might have significant anti-inflammatory as well as anti-atherogenic effects as measured by endothelial function, nitric oxide formation and other parameters. So I don't think that the traditionally high doses are the ones that necessarily would need to be done. But I don't want to debate whether we should be studying doses of 4 grams of aspirin.

DR. WOOD: What you are telling us, Charlie, is that you are comfortable that there is an antithrombotic effect at the high doses of aspirin. Is that right? Okay. Good. Dr. Cush wants to say something.

DR. CUSH: Again, you need not anti-inflammatory doses but analgesic doses which can be substantially lower. I do want to make a statement with regard to a study that wasn't presented here that I think is germane and we should know about it, and this is quick. There is a very large trial that is NIH supported that is called the GATE study, glucosamine in osteoarthritis of the knee. This is a 1588 study that is completed and is currently being analyzed. That

Data Safety Monitoring Board of the study has analyzed it for cardiovascular risk because there is a Celebrex arm. There are five arms in this 1500-patient study; placebo, Celebrex 200 milligrams once a day, glucosamine only, chondroitin sulfate only, and glucosamine and chondroitin sulfate. The outcome here, in a six-month trial, is pain reduction in osteoarthritis in the

knee. Because of all this press and what not, they have looked at the safety outcomes and they have not shown any increase in cardiovascular events including M.I., any difference between the Celebrex group and the other four control groups.

DR. WOOD: Let's move on to the program. Dr. Hertz?