

**A**fter all 3 presentations from Drs. Kavanaugh, Wolfe, and Ward were concluded, a brief question-and-answer session took place among all symposium participants.

**Question:** Most of us have that interesting tension in that we are health-care providers but we're also representing a business. To look from a business side, I'm concerned, because if I look at the reported cost of infliximab—about \$6000 a year—I don't know whether that represents 2 doses in a 6-month period or if it's more doses, but that cost would represent about \$60 million for Blue Cross of California if we're assuming that about one fifth of a percent of the population would require more significant treatment. That's a lot of dollars.

Are there any good data to show that the etanercept responders will also be good infliximab responders? Are there markers to determine which serious rheumatoid arthritis (RA) patients will respond to these treatments?

**Dr. Kavanaugh:** That is a key question and I think we'd all like to say there are patients who do respond exceptionally well. We've seen people who were really not functioning but now after treatment are gardening and working and are pretty much back to a normal life. But it's a real challenge to identify them. You look at numbers of affected joints, sedimentation rates, prevalence, and demographics, but those things don't seem to clearly differentiate responders from nonresponders.

A lot of the information we collect routinely in the clinic doesn't look as

if it's going to be able to predict the specific people who are going to have a good response and among those, this person's going to have a particularly good response. So yes, that is going to be a challenge.

And of course one of the main reasons we're here today is to talk about cost. You do have some initial sticker shock, I think, in part because RA has been relatively cheap to treat so far. But indirect costs need to be considered as well. For example, we are able to treat people less expensively with prednisone and nonsteroidals. Those drugs can be cheap, but the side effects can be very expensive. So I think you have to take into account all the factors. On some level, though, it's also going to get down to deciding how much it is worth to us to have someone feel better. That's a very tough issue.

**Comment:** In the managed care environment we have other extraneous pressures such as pressure from patients to continue with a drug even when there is very little improvement. If you try to remove that drug, the patient often sees that as having a benefit withdrawn because they are in a managed care environment. It is sometimes very difficult to get patients away from the frame of mind that says, "If I try it a little longer and a little longer, then it will work." That's one of the major problems we as medical directors have in trying to manage this type of problem in a managed care environment.

If a medicine is effective, you're going to have a lot of people who will want to try it and it's hard to see how you are going to say no to some. But

some people are going to get only minimal benefit from it and with a chronic, painful disorder like this, we're going to get enormous pressure to continue the drugs anyway.

Additionally, I'm concerned about side effects. We don't know what to expect long term, nor how long we can use these.

**Dr. Wolfe:** Side effects are obviously something we'll have to monitor carefully. One of the things about the demographics of the people who have been studied is that they have the most severe RA. Those with the most severe RA are also going to have bad outcomes in terms of sepsis, and in terms of the development of lymphoproliferative malignancies. So at this point, it's hard to dissociate. There doesn't seem to be a tremendous excess of either of these disorders, apart from what you'd expect, from the group of treated patients.

Now that etanercept is being given to many thousands of patients outside of clinical studies, we are seeing the development of sepsis, but you would see that with patients treated with other immunosuppressants as well. That's just something we'll have to watch for.

We also need to determine that if we can use these drugs to get someone to a state of very minimal disease activity, can we then substitute the treatment with something cheaper? We don't know yet; it hasn't been done. In the trials, etanercept and infliximab were used as monotherapy. When the monotherapy was stopped, the disease came back. Now we're trying to gather data to help us determine if we're able to sustain a good response if someone on an anti-tumor necrosis factor alpha (TNF $\alpha$ ) blocker is withdrawn from it and put on a high dose of methotrexate. So that's something among the many things we need to learn.

**Comment:** I kind of take issue with the statement that the treatment of RA

is cheap. I think we've seen some good data that show it has been expensive. If you look at the gastrointestinal (GI) bleed rate with the use of nonsteroidal anti-inflammatory drugs (NSAIDs), the cost of some of the GI agents that are used in addition to NSAIDs, the COX-2 (cyclo-oxygenase-2) inhibitors, the cost of orthopedic treatment, physical therapy, and assistive devices, you'll see that treating RA is not cheap. The disease-modifying antirheumatic drugs (DMARDs) may be relatively cheap, but the total cost of RA is actually high because the disease itself has a very high morbidity.

**Dr. Ward:** Right, and so the question then becomes not a question of cost but a question of value, right? And are we appropriately evaluating the quality of life of those who have RA?

The suggestion has been put forth that part of the problem in evaluating the costs of treatment with RA is that 75% to 80% of the patients are women. That may be a substantial obstacle in establishing the value of what society is willing to pay to get these people to feel better.

**Question:** Dr. Wolfe, using the predictor factors you have, and treating those people who would be on the most serious curve very aggressively over a period of time, can you show that that curve shifts, or is there a biologic predetermination to the disease?

**Dr. Wolfe:** Well, certainly there is a biological predetermination to severity, and you can often pick out those people who are going to do poorly pretty early on. But I think there is almost no question that when one gets therapy that reduces the burden of inflammation of disease, costs are going to be reduced down the road in terms of avoiding surgery and work disability.

**Question:** Dr. Ward, in your discussion, you talked about Kaiser and you

alluded to the fact that these data may not translate to other managed care environments, but knowing what the data mean to Medicare and the pharmacy benefit is critical. Many Medicare managed care plans have fairly significant pharmacy caps that might mean, in terms of the therapies we are talking about, that people would either have to purchase a supplemental plan, or self pay. I wonder whether that may be a more compelling variable that needs to be evaluated than simply whether or not the treatment was covered by managed care or fee-for-service.

*Dr. Ward:* There was actually a study published in *JAMA* approximately 2 years ago that looked at that question. It asked Medicare enrollees, who were either in fee-for-service or HMO practice settings, what their health outcomes were. One of the symptom conditions they tracked was chronic joint pain. There were no differences in the types of treatment used, but the people in the managed care group saw a physician for the problem more often than did people in the indemnity insurance group. But they actually had a lower proportion of complete resolution of the problem, and less follow up, than people in the indemnity group. That's an indication that as managed care extends into more diverse demographic groups, the outcomes may not be as comparable as the ones we have.

If you look at all of the studies comparing health outcomes in managed care and fee-for-service settings, there are incredibly few differences. That ranges from breast cancer to coronary heart disease to every condition you could imagine. Whether or not this continues as more and more people move into managed care plans is anybody's guess. But I would be cautious in making sweeping generalizations.

There are some important issues regarding frequency of visits and whether or not patients are seen by

rheumatologists. There are several published pieces that show costs can be cut by as much as a third if patients are permitted more frequent visits with rheumatologists.

So frequency is important in decreasing costs and I think we all see that if you can get patients good access to rheumatologists, then we may not have to worry about using drugs like etanercept. If we treat quickly and aggressively, then maybe they won't progress to needing these drugs. If after 5 or 10 years such aggressive treatment prevents a hip or knee replacement, that's going to mean a big savings to health plans.

*Question:* I'm very interested in some of the pharmacology of the drugs and in finding out how we know, for instance, over 4 or 8 weeks, that a dose of 3 mg/kg or 10 mg/kg had no significant differences. What about extending the dose interval, or decreasing the dose? Won't there be people who might have a partial response or a suboptimal response on 3 mg/kg and do better on 10 mg/kg? At some point, as you lower the dose, you do decrease the extent of efficacy, not just the duration. Most of the dose effect seems to be on duration; it doesn't affect the pharmacokinetics. But 1 mg/kg is clearly inferior to 3 mg/kg or to 10 mg/kg.

*Dr. Kavanaugh:* From the earliest studies when it was used as monotherapy, it was probably just the pharmacokinetics so with the 1 mg/kg, the parameters returned to what they were. The patients appeared to go back to extended disease. That happened within 4 to 5 weeks on the 1 mg/kg. It was more than 12 weeks on the 10 mg/kg as a mean. So obviously there are outliers on either end.

*Comment:* The kinds of patients we'll be seeing in our environments are patients who are not doing particular-

ly well on a more traditional regimen. And chances are physicians wouldn't stop a regimen in which the patients were only partially responding, but would instead add therapy.

**Dr. Kavanaugh:** I think that's happening a lot in the clinic—people are being treated with one kind of therapy and then others are added on top. Now the question is going to be if you can make a more dramatic difference by treating aggressively with something this powerful early on in the disease process. Will doing so help to keep the person from incurring disability?

**Question:** I read some things before this meeting that implied that intermittent therapy might be associated with the development of antibodies that might interfere with efficacy over the long term. What do you think about that? That would have some cost ramifications also.

**Dr. Kavanaugh:** Part of the compound is foreign. If one was going to design a treatment with the goal of getting a response—like a vaccination—the way to do it would be to intermittently administer it and then give the memory cells a chance to react. So giving it once every 6 months would probably not be a reasonable strategy because that could increase immunogenicity, which would have implications in terms of the pharmacokinetics and efficacy and maybe also in terms of adverse effects. Using it on a long-term, regular schedule would certainly be preferable. That's going to be true for

any compound that has a foreign component to it.

**Comment:** Because infliximab is a cytoreceptor it may be that very low doses in most people will actually make the disease worse. That's probably more a property of cytoreceptors than an antibody to TNF.

**Question:** In using so many different agents that have a wide range along the cost scale, what seems to be the cut off price points at which patients or administrators balk or say "I'm not going to pay that kind of money"?

**Dr. Ward:** I think we've hit it for sure. I don't know if it's that so many new drugs are being introduced to rheumatology at the same time, but all of them are raising eyebrows.

**Dr. Wolfe:** The hardest-hit group of rheumatic disease patients are those who are in their 50s, who suddenly get very ill and lose their jobs but don't have insurance. They can't afford any of these drugs. And we certainly have Medicare patients who have said, "I can't afford to take this medication."

Last year we did a survey of about 1500 RA patients that asked if they had problems paying for their medications. We gave them 3 choices for answers that basically said, "no problem," "a little bit of a problem, but I can do it," and "I can't do it." Only 8% of respondents said they couldn't pick up the medications. The people who couldn't afford their drugs tended to be those who were over 65.