OPPOSITE attracts? Rationalizing therapy in rheumatology

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Rationalization of therapy in rheumatology has huge potential benefits. Daniel Furst is at the forefront of those seeking to improve the ways that change can be measured in rheumatic diseases in order to provide optimal therapy. Furst also led the OPPOSITE trial and published the findings earlier this year. Furst is the Carl M Pearson Professor of Medicine and Director of the Rheumatology Clinical Research Center at the University of California, Los Angeles (UCLA), CA, USA. He received his medical degree from Johns Hopkins University, MD, USA, in 1968 and completed fellowships in Clinical Pharmacology at the University of California, San Francisco and in Rheumatology at UCLA. His research interests are in the clinical pharmacology of drugs used to treat rheumatic and autoimmune diseases, including nonsteroidal anti-inflammatory drugs, disease-modifying antirheumatic drugs and biological modifiers. Here he discusses the approaches towards rationalizing therapy and highlights some future directions.

Why rheumatology?

My background is not only in rheumatology but also in clinical pharmacology and I completed fellowships in both these areas. My dedication to rheumatology developed when I was exposed to a really wonderful teacher, Professor Mary Betty Stevens, when I was in medical school at Johns Hopkins. She made rheumatology seem like the most interesting area in the world and has also inspired many other very well known rheumatologists. When I moved into my residency it became clear to me that there was a huge need in rheumatology; there was so little that we knew and so many patients having so much trouble. All these factors led me into the field.

In terms of my specific interests, one particular research focus is on the rationalization of therapy in the rheumatic diseases and how to improve the way in which we measure change. If one cannot measure a change following treatment then one cannot monitor the effectiveness of a treatment. I am also studying the use of new medications both to help patients in a rational way and to help understand the pathogenesis of disease. Analyzing the pathways by which a well-targeted medicine works can do a great deal to help us to understand the pathogenesis of that disease.

The recently published OPPOSITE trial, for which you were lead author, attracted a lot of interest. What were the main aims & findings?

There were basically three aims to this study. First, can an increased dose of etanercept improve a patient response? Second, can one later withdraw that increased dose back to a standard dose and maintain the same response? Third, are there any ways that can help predict the response based on initial measurements?

We performed some good pharmacokinetics in the study, which showed that increasing the dose doubled the blood level of etanercept and that this had no effect on response. The study demonstrates that, at least by 12 weeks, doubling the dose of etanercept does not improve response. We still have to undertake some work to see if there is any improvement in the first few weeks of therapy, on the basis that a loading dose may possibly do that. However, at the moment I would say that there is really no good reason to raise the dose of etanercept in this way.

The answers provided by this trial helped us immensely but not in the way that we had expected. The main finding of this short-term, double-blind trial was that increasing the dose of etanercept in a patient who has not been responding to normal doses of therapy does not help. This should lead to changes in the way patients are treated, since many physicians use very high doses of etanercept for which there is no justification. Administering the lower doses will drastically decrease the cost of treating patients.

How would the improvement of the ACR response criteria affect the development of new drugs?

First, the recent iteration of this particular measurement of change is only an interim one; there are going to be further changes. However, I think that this importantly increases attention to patient factors. The Disease Activity Score, using

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28 joint counts (DAS-28), provides an excellent continuous measure of change. However, patient factors account for only approximately 2% of the total measurement with the DAS-28 whereas the ACR improvement has a much larger component of patient factors. Thus, further iterations of the ACR Response Criteria are going to include much more information about how patients themselves feel.

Second, this, and other similar measures that are being developed, will increase our ability to find an effective drug. The reasoning behind this is twofold. It allows us to evaluate the sensitivity of measurements of change and, as the measurement is continuous and has a normal distribution, it has more statistical power, which allows us to identify differences more easily in small numbers of patients.

What effect do you think the high-profile withdrawal of rofecoxib & rejection of etorocoxib by the US FDA will have on future development of COX-2 inhibitors?

First, although people say that NSAIDs and COX-2 inhibitors have a high frequency of adverse events, I would say that this is overstated. They certainly have adverse effects, as with many drugs, but as I always tell my patients, you never get something for nothing. NSAIDs actually have a very good therapeutic index – I think that one of the problems with these drugs is that a great deal has been made about relative risk and not enough about absolute risk. This is an important concept; for example, let us imagine that you have a drug that has a serious side effect in one in 10,000 patients and you have another drug that has an occurrence of the same side effect four-times in 10,000. The relative risk is four but the absolute risk is no more than three per 10,000 patients. Although the relative risk sounds awful, for any given patient the increased real risk is actually very small. I think that there remains an important need to allow further NSAID/COX-2 choices for individual patients. These regulatory actions, driven I'm afraid by a great deal of risk-averse behavior, will decrease the choices for individual patients, since these actions will have a major effect on the development of COX inhibitors, particularly in the USA and probably worldwide. This will lead to fewer choices of NSAIDs that have an advantage in selected patients.

The cardiovascular risk has been emphasized and the importance of the reduced gastrointestinal (GI) risk has been diluted. I'm afraid that the American Health Association (AHA), through a paper that it has published, has done a major disservice to patients, particularly the elderly. For example, the AHA position is that narcotics should be used rather than NSAIDs. This presents a serious problem, since an older patient on narcotics has an increased risk of falling and breaking their hips, and the mortality of hip fractures in elderly patients is extraordinarily high.

Could the best features of the NSAID &COX-2 inhibitors be combined to produce safer anti-inflammatory/analgesics?

I think this is a very good and very hard question. One could try some combinations of medications to try and circumvent the side effects and still achieve the positive effects. One that has been tried and has not yet gotten very far is the confirmation of an NSAID with nitrogen oxide (NO); NO results in vasodilatation and protection of the stomach and consequently potentially allows an increased positive effect without the side effects. This kind of approach may prove quite useful.

How will you focus your future research?

Still within the context of looking at measurements of change, a major effort is required to rationalize the measurement of toxicity. Currently, toxicity is measured by simply listing the toxicities and assigning percentages, whereas efficacy is measured by combination measures that result in a single number reflecting overall efficacy. We need to work towards a way to measure toxicity in the same way. Another particular area of interest from my point of view will be looking at the GI tract in rheumatic disease, particular scleroderma.

I am also working on increasing the standard of clinical research in developing countries. For example, I am involved in a study in India comparing methotrexate and ayurvedic medicine. The involved Indian researchers are very smart people who simply need a little help with the basics. This effort is fantastic and rewarding and we are going to learn a lot, so this is an area in which I intend to spend much more time and effort.

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