RA Drug Trials Often Lack Active Comparator

The proposal is to change the trial design to substitute an active comparator for the placebo.

BY MITCHEL L. ZOLER

FROM THE ANNUAL EUROPEAN CONGRESS OF RHEUMATOLOGY

LONDON – Many recently performed rheumatology drug trials have run into the ethical trap of treating control patients with an ineffective regimen, with the result that some patients experienced ongoing pain and joint dysfunction and continued disease progression.

"I would propose that we change the trial design for the placebo control to use an active comparator against the [investigational] drug," Dr. Aaron Juche said while presenting a poster at the meeting.

For studies testing a new drug aimed at controlling rheumatoid arthritis pain, dysfunction, and progression, "the standard of care would be a tumor necrosis factor [TNF] inhibitor as the active comparator," said Dr. Juche, a rheumatologist at Johanniter Hospital in Treuenbrietzen, Germany. Because TNF inhibitors are so effective, a study that uses this treatment in the comparator arm would likely have to be a noninferiority study and would also probably have to involve a relatively large number of patients, he said in an interview.

The standard approach for drug-trial design in patients with RA in recent years has been to follow a model that's more than a decade old, dating back to the first studies on TNF inhibitors during the 1990s: "Patients who did not adequately respond to immunosuppressive drugs were randomly assigned to either an experimental condition under which they received the new substance, or to a control condition under which they continued their formerly inefficient treatment and received a placebo."

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New drugs should be compared with a TNF inhibitor, suggested Dr. Aaron Juche.

To more systematically assess the scope of the problem, he and his associate reviewed 17 recent, published clinical trials that drug companies used to document the safety and efficacy of three new drugs, abatacept, golimumab, and tocilizumab, to the European Medicines Agencies. Dr. Juche said these studies fairly represented most recently performed drug efficacy trials for patients with RA.

Of the seven studies he reviewed that tested abatacept, none used a control therapy that effectively treated the patients' disease. In all seven studies, patients remained on treatment with a disease-modifying antirheumatic drug (DMARD) that they had already failed on, most commonly methotrexate. During these studies, "patients experienced a persistent, high disease activity," he reported.

Among four pivotal studies involving golimumab, one enrolled methotrexate-naive patients and then used methotrexate as the control drug. The other three used control groups that received placebo and nothing else or placebo plus methotrexate for enrolled patients who had already failed methotrexate.

A similar pattern existed for the six studies of tocilizumab that Dr. Juche reviewed.

One of the six used methotrexate as the comparator in a trial that enrolled methotrexate-naive patients. The other five studies used comparator groups on either placebo alone or placebo plus a DMARD to which the patient had already not responded.

Dr. Juche added that rheumatology is not unique in having so many of its trials involve ineffective regimens in the control groups. ■

VITALS

Major Finding: A review of 17 recent clinical trials for three new rheumatoid arthritis drugs showed that only two of the trials placed patients randomized into the comparator arms on active drug regimens.

Data Source: Review of publicly reported trial data.

Disclosures: Dr. Juche said that he has received travel support from Actelion.

Opioid Rotation: Convert Tx With Safety-Focused Approach

BY SHARON WORCESTER

EXPERT ANALYSIS FROM THE CONGRESS OF CLINICAL RHEUMATOLOGY

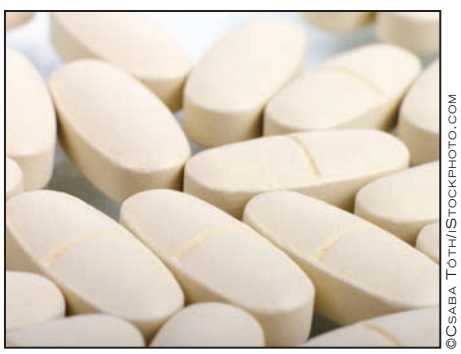
DESTIN, FLA. – Opioid rotation is a common and potentially beneficial practice for helping to relieve chronic pain in patients who require ongoing opioid therapy, but there are very few data to guide best practice.

The recommended approach, therefore, is one that focuses on safety, according to Dr. Perry Fine. Clinicians should consider opioid rotation when patients on chronic opioid therapy experience intolerable adverse effects, or when benefits are inadequate despite dose increases, according to recently published clinical guidelines (J. Pain 2009;10:113-30).

However, it is important to consider a number of factors before making changes in treatment, including demographic, disease-related, and treatment-related factors, as well as comorbidities, concomitant pharmacotherapy, drug sensitivities, and social situation, said Dr. Fine, professor of anesthesiology at the University of Utah, Salt Lake City.

If a decision is made to convert a patient's treatment, a two-step, safety-focused approach is needed, he said.

Step 1 involves an "automatic safety factor" calculation. That is, the equianalgesic dose of the new opioid should be calculated via an equianalgesic table such as a mu-agonist dose chart, and, with a few exceptions, an automatic dose reduction of 25%-50% should be made, except if the new drug is methadone or transdermal fentanyl.



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Consider opioid rotation when benefits are inadequate despite dose increases.

A 25% reduction for opioids (other than methadone or fentanyl) is adequate in patients with no risk factors and/or if the switch is to a different route of administration of the same drug. A 50% reduction is needed in those receiving a relatively high dose of the current opioid, those who are elderly or frail, and those of Chinese lineage, Dr. Fine said.

If the switch is to methadone, a 75%-90% dose reduction is needed, and if the switch is to transdermal fentanyl, use the reduction that is built into the conversion charts provided in the prescribing information. If an oral transmucosal fentanyl citrate formulation is used, start with the lowest dose, he advised.

The second conversion step involves patient-specific adjustments. The patient should be assessed for pain severity and other medical or psychosocial characteristics, and appropriate additional adjustments should be made to the initial dose of the new opioid.

In patients with specific vulnerabilities such as advanced age, renal insufficiency, or cognitive impairment, consider an additional 10%-30% dose reduction, he said.

Dr. Fine has served as an advisory board member for Ameritox, Covidien, King (now Pfizer), Meda, and Purdue-Pharma. He also is a consultant for Cephalon and Johnson & Johnson. ■

Examples of Initial Dose Calculation

► To convert controlled-release oxycodone (60 mg oral dose twice daily) to controlled-release morphine:
1. Calculate the total oxycodone 24-hour dose (120 mg).
2. Determine morphine equivalency (20 mg oxycodone = 30 mg morphine).
3. Convert the 24-hour oxycodone dose to the morphine dose (120 mg oxycodone = 180 mg morphine).
4. Reduce the morphine dose by 25% (135 mg morphine).
5. Split the total morphine dose to the twice-daily dose (67.5 mg). Because the controlled-release (extended-release) morphine is not provided in this exact dose, give the closest available dose (60 mg, twice daily).

► To convert controlled-release morphine (30 mg oral dose twice daily) to transdermal fentanyl:
1. Calculate the total morphine 24-hour dose (60 mg).
2. Use the prescribing info. to determine the oral equivalent dose of transdermal fentanyl (60 mg oral morphine = 25 mcg/hr fentanyl patch).
3. Prescribe 25 mcg/hr transdermal fentanyl patch to be changed every 3 days. Supply patient with five patches (a 15-day supply); instruct patient on application, and follow up by phone or in office within 2-3 days.

► To convert methadone (20 mg oral dose three times daily) to extended-release oxymorphone:
1. Calculate the total methadone 24-hour dose (60 mg daily).
2. Use mu-agonist dose chart to calculate oxymorphone dose equivalency to methadone (5 mg methadone = 10 mg oxymorphone).
3. Convert the 24-hour methadone dose to oxymorphone dose (60 mg methadone = 120 mg oxymorphone).
4. Reduce the dose by 50% and split the 50% total calculated oxymorphone dosage to a twice-daily dose. Prescribe oxymorphone ER (30 mg oral dose every 12 hours).

Source: Dr. Fine