

Etanercept Eased AS Symptoms in ESTHER

Growing experience with biologics provides data on how to predict response in ankylosing spondylitis.

BY SHARON WORCESTER

EXPERT ANALYSIS FROM THE CONGRESS OF CLINICAL RHEUMATOLOGY

DESTIN, FLA. – A finding that the response to etanercept is markedly better than the response to sulfasalazine among patients with ankylosing spondylitis is one of a number of recent developments regarding the treatment of the disease, according to Dr. Robert Inman.

Among other developments Dr. Inman discussed were new findings regarding predictors of response to treatment, the effects of switching biologics, the effects of discontinuing biologics, and the use of newer biologics for ankylosing spondylitis (AS).

The etanercept findings are from the recently published 48-week randomized controlled ESTHER trial (Effects of Etanercept Versus Sulfasalazine in Early Axial Spondyloarthritis on Active Inflammatory Lesions as Detected by Whole-Body Magnetic Resonance Imaging).

The percentage of patients in the etanercept vs. sulfasalazine groups who achieved 20% improvement, 40% improvement, or partial response based on Assessment in SpondyloArthritis International Society (ASAS) criteria were 85% vs. 42% (ASAS20), 70% vs. 31% (ASAS40), and 50% vs. 19% (ASASpR), respectively. The percentage of patients in the etanercept vs. sulfasalazine groups who achieved 50% improvement on the Bath Ankylosing Spondylitis Disease Ac-

tivity Index (BASDAI50) were 65% vs. 28% (Ann. Rheum. Dis. 2011;70:590-6).

"Etanercept far outperformed sulfasalazine," said Dr. Inman, professor of medicine at Toronto Western Hospital.

Another study, published online in March in Annals of the Rheumatic Diseases, showed that clinical predictors of response to treatment in AS patients include age, presence or absence of human leukocyte antigen B27 subtype (HLA-B27), Bath Ankylosing Spondylitis Functional Index (BASFI) score, and the presence or absence of enthesitis (Ann. Rheum. Dis. 2011;70:973-81).

"This is just clinical bedside analysis," he said, noting that the findings suggest that an ideal patient for treatment would be a young patient with no enthesitis who is B27 positive and who has a low BASFI. The response rate in such a patient, based on the data, would be well over 80%, but that's not to say patients without all of these characteristics will not respond.

"We've certainly had patients (outside of this ideal group) who have had a great response," he said.

As for switching and discontinuing biologics, one study reported at the American College of Rheumatology meeting in 2009 (ACR 2009), which assessed outcomes in patients who switched to a second tumor necrosis factor (TNF) inhibitor after failing the first, showed that switchers achieved a reasonable response. Switchers achieved more than half the response rate (about 30%) of

that achieved by nonswitchers (49%), but the percentage of patients achieving ASAS20 on the second anti-TNF (52% of nonswitchers and 44% of switchers) was "actually not bad ... so there's certainly grounds for switching," Dr. Inman said, noting that there are enough data in the literature to support that.

Another study reported at ACR 2010 showed that infliximab had continued efficacy in HLA-B27 patients with very early AS even after discontinuation before 16 weeks. About 40% of patients treated with infliximab did not flare through week 40 following drug withdrawal.



A patient who has failed an anti-TNF is unlikely to respond to rituximab, despite its mechanism of action.

DR. INMAN

"So there may be a subset of patients who, if you capture control very early on, you might be able to switch," he said.

Several recent studies also have assessed newer biologics for the treatment of AS – with mixed results.

In a disappointing open-label 24-week study of abatacept reported at EULAR 2010, for example, the ASAS20, ASAS40, ASASpR, and BASDAI50 responses in 15 anti-TNF naive patients were 26.7%, 13.3%, 6.7%, and 6.7%, respectively. The only response seen among 15 patients who failed a prior anti-TNF was on the ASAS20, with 20% of patients responding at this level.

"So abatacept does not have a very encouraging signal in ankylosing spondylitis," Dr. Inman said.

Rituximab, however, was shown in a study presented at EULAR 2009 to be associated with good responses at week 24 of treatment. ASAS20, ASAS40, and BASDAI50 response rates were 50%, 40%, and 50%, respectively, in anti-TNF treatment naive patients, and 30%, 10%, and 0%, respectively, in those who failed a prior anti-TNF drug.

While these response rates aren't quite as good as those seen with anti-TNFs, they are fairly good, and suggest that rituximab is a reasonable choice, particularly in patients with a relative contraindication to an anti-TNF, he said.

However, in a patient who has failed an anti-TNF drug, it's "very unlikely you're going to hit a home run with rituximab," he added.

Another agent – the anti-IL17A monoclonal antibody secukinumab (AIN57) – was shown in a proof-of-concept study presented at ACR 2010 to be associated with substantially greater ASAS20 response in 30 patients with active AS, compared with placebo (60% vs. 17%). Responses were seen within 1 week in most of the patients.

However, while the response rate was significantly higher than with placebo, the relative change in BASDAI50 was relatively modest and not of the same magnitude typically seen with anti-TNF drugs, he said.

"So I think the jury is still out on the anti-IL17," he concluded.

Dr. Inman disclosed that he is a consultant for Abbott Laboratories, Merck, Pfizer, and Sanofi-Aventis. ■

Titration is Key to Methadone's Safe Use for Chronic Pain

BY SHARON WORCESTER

EXPERT ANALYSIS FROM THE CONGRESS OF CLINICAL RHEUMATOLOGY

DESTIN, FLA. – Methadone can be an effective treatment for chronic pain, but there are a number of concerns that must be considered when prescribing this opioid, according to Dr. Perry G. Fine.

Among the benefits of the effective mu-opioid analgesic with N-methyl-D-aspartate receptor antagonist properties are its low cost, dosing formulation versatility, long duration of action, and favorable metabolic profile. However, it also has highly variable pharmacokinetics, a very long half-life compared with its analgesic duration of action, and non-linear dose conversion.

Prescribing this drug requires methadone-specific knowledge and vigilance on the part of the prescriber, as well as a highly responsible patient and/or caregiver who will monitor use and side effects, particularly during titration, according to Dr. Fine, professor of anesthesiology at the Pain Research Center, University of Utah, Salt Lake City.

Potential problems with methadone include drug-drug interactions and cardiac toxicity. Sudden death,



even at therapeutic levels, can occur.

Drug-drug interactions can include adverse reactions in patients on monoamine-increasing drugs. Also, serum levels are increased by CYP3A4 and CYP2B6 inhibitors (such as certain antiretrovirals, clarithromycin, itraconazole, erythromycin, fluconazole, grapefruit juice, and more), and this has been associated with multiple overdose deaths, prompting a black-box warning advisory in 2006, Dr. Fine said.

Older patients or those with renal or hepatic problems need less frequent dosing and more cautious titration.

DR. FINE

Potential cardiac toxicity is the newest concern; treatment has been shown in some patients to prolong the corrected QT (QTc) interval, and while prescribing guidelines do not yet reflect this, a baseline electrocardiogram is advisable, Dr. Fine said. According to current guidelines from the American Pain Society–American Academy of Pain Medicine, a reasonable starting dose in most opioid-naïve patients is 2.5 mg every 8 hours. Dose increases can begin after a minimum of 10 days. Older patients, or those with renal or hepatic comorbidities, require less frequent dosing, and more cautious dose titration. Methadone treatment is not advisable for breakthrough pain because of its long half-life and variable pharmacokinetics (J. Pain 2009;10:113-20).

Titration, according to Dr. Fine, should include dose

increases of 1-2.5 mg every 8 hours in frail, older patients or patients with a history of sleep apnea, and 2.5-5 mg every 8 hours in robust younger patients. Increases should be made every 5-7 days if needed.

Advise patients or caregivers that:

- ▶ Adequate pain relief from methadone may not occur for several days or weeks.
- ▶ Methadone should be taken exactly as directed.
- ▶ Short-acting rescue medications can be used until sufficient baseline analgesia is achieved.
- ▶ Any signs of increased sedations, mental clouding, snoring, or periodic apnea should be called in (supply an emergency phone number).
- ▶ No alcohol, benzodiazepines, or other CNS depressants should be used – especially at night – unless specifically prescribed or approved by the physician who prescribed the methadone.

Also, follow up every day during dose titration by a telephone call, through home nursing, or by an office visit, and perform an in-person evaluation weekly until dose stabilization and then monthly thereafter if there are no major ongoing changes in health status, Dr. Fine said.

In-person evaluations should be performed every 3 months once the patient is fully stable, he added.

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