

# Gains Seen in Ankylosing Spondylitis; Dx Lags

BY BRUCE K. DIXON

Chicago Bureau

CHICAGO — Early treatment of ankylosing spondylitis may or may not prevent structural damage but it certainly improves quality of life and the ability to function, Dr. John Davis told a symposium of the American College of Rheumatology.

Dr. Davis pointed to four reasons for why ankylosing spondylitis (AS) is typically diagnosed about 8 years after disease

onset: low awareness of the spondyloarthritis among nonrheumatologists; the erroneous belief among rheumatologists that AS is a “man’s disease”; the difficulty in differentiating between mechanical and inflammatory back pain; and reliance on radiologic sacroiliitis, which is a late feature of AS.

Dr. Davis, who directs the Clinical Trials Center at the University of California, San Francisco, noted that the Spondylitis Association of America guidelines call for

a thorough physical exam including x-rays, individual medical history, and any family history of AS, as well as blood work that includes a test for HLA-B27 antigen. Important signs of AS include pain that has persisted longer than 3 months, back pain, and stiffness that worsen with immobility but ease with physical activity, and a positive response to NSAIDs.

Research efforts are now focusing on three TNF inhibitors. Phase III trials of

three biologics showed good responses that were maintained at over 2 years (etanercept and infliximab) and 24 weeks (adalimumab). All three drugs significantly outperformed placebo in phase III studies using the Assessment in AS (ASAS) International Working Group criteria and the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI). The BASDAI form contains six visual analog scales (“none” to “very severe”) on fatigue, neck, back or hip pain, joint pain and swelling, tender areas, and morning stiffness. “If you use the BASDAI as an outcome measure you should expect about a 50% improvement in the BASDAI 50 in all the anti-TNF studies,” Dr. Davis explained, adding that

## ULTRAM<sup>®</sup> ER

(tramadol HCl) Extended-Release Tablets

Rx only

**BRIEF SUMMARY. CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION. INDICATIONS AND USAGE:** ULTRAM ER is indicated for the management of moderate to moderately severe chronic pain in adults who require around-the-clock treatment of their pain for an extended period of time. **CONTRAINDICATIONS:** ULTRAM ER should not be administered to patients who have previously demonstrated hypersensitivity to tramadol, any other component of this product or opioids. ULTRAM ER is contraindicated in any situation where opioids are contraindicated, including acute intoxication with any of the following: alcohol, hypnotics, narcotics, centrally acting analgesics, opioids or psychotropic drugs. ULTRAM ER may worsen central nervous system and respiratory depression in these patients.

**WARNINGS:** Seizure Risk: Seizures have been reported in patients receiving tramadol within the recommended dosage range. Spontaneous post-marketing reports indicate that seizure risk is increased with doses of tramadol above the recommended range. Concomitant use of tramadol increases the seizure risk in patients taking: 1. Selective serotonin re-uptake inhibitors (SSRI antidepressants or anorectics), 2. Tricyclic antidepressants (TCAs), and other tricyclic compounds (e.g., cyclobenzaprine, promethazine, etc.), or 3. Other opioids. Administration of tramadol may enhance the seizure risk in patients taking: 1. MAO inhibitors (see also WARNINGS - Use with MAO Inhibitors), 2. Neuroleptics, or 3. Other drugs that reduce the seizure threshold. Risk of convulsions may also increase in patients with epilepsy, those with a history of seizures, or in patients with a recognized risk for seizure (such as head trauma, metabolic disorders, alcohol and drug withdrawal, CNS infections). In tramadol overdose, naloxone administration may increase the risk of seizure.

**Suicide Risk: 1. Do not prescribe ULTRAM ER for patients who are suicidal or addiction-prone. 2. Prescribe ULTRAM ER with caution for patients taking tranquilizers or antidepressant drugs and patients who use alcohol in excess. 3. Tell your patients not to exceed the recommended dose and to limit their intake of alcohol.**

Tramadol products in excessive doses, either alone or in combination with other CNS depressants, including alcohol, are a major cause of drug-related deaths. Fatalities within the first hour of overdose are not uncommon. Tramadol should not be taken in doses higher than those recommended by the physician. The judicious prescribing of tramadol is essential to the safe use of this drug. With patients who are depressed or suicidal, consideration should be given to the use of non-narcotic analgesics. Patients should be cautioned about the concomitant use of tramadol products and alcohol because of potentially serious CNS-addictive effects of these agents. Because of its added depressant effects, tramadol should be prescribed with caution for those patients whose medical condition requires the concomitant administration of sedatives, tranquilizers, muscle relaxants, antidepressants, or other CNS-depressant drugs. Patients should be advised of the additive depressant effects of these combinations. Many of the tramadol-related deaths have occurred in patients with previous histories of emotional disturbances or suicidal ideation or attempts as well as histories of misuse of tranquilizers, alcohol, and other CNS-active drugs. Some deaths have occurred as a consequence of the accidental ingestion of excessive quantities of tramadol alone or in combination with other drugs. Patients taking tramadol should be warned not to exceed the dose recommended by their physician.

**Anaphylactoid Reactions:** Serious and rarely fatal anaphylactoid reactions have been reported in patients receiving therapy with tramadol. When these events do occur it is often following the first dose. Other reported allergic reactions include pruritus, hives, bronchospasm, angioedema, toxic epidermal necrolysis and Stevens-Johnson syndrome. Patients with a history of anaphylactoid reactions to cocaine and other opioids may be at increased risk and therefore should not receive ULTRAM ER (see CONTRAINDICATIONS).

**Respiratory Depression:** Administer ULTRAM ER cautiously in patients at risk for respiratory depression. In these patients alternative non-opioid analgesics should be considered. When large doses of tramadol are administered with anesthetic medications or alcohol, respiratory depression may result. Respiratory depression should be treated as an overdose. If naloxone is to be administered, use cautiously because it may precipitate seizures (see WARNINGS - Seizure Risk and OVERDOSAGE).

**Interaction With Central Nervous System (CNS) Depressants:** ULTRAM ER should be used with caution and in reduced dosages when administered to patients receiving CNS depressants such as alcohol, opioids, anesthetic agents, narcotics, phenothiazines, tranquilizers or sedative hypnotics. ULTRAM ER increases the risk of CNS and respiratory depression in these patients.

**Increased Intracranial Pressure or Head Trauma:** ULTRAM ER should be used with caution in patients with increased intracranial pressure or head injury. The respiratory depressant effects of opioids include carbon dioxide retention and secondary elevation of cerebrospinal fluid pressure, and may be markedly exaggerated in these patients. Additionally, pupillary changes (miosis) from tramadol may obscure the existence, extent, or course of intracranial pathology. Clinicians should also maintain a high index of suspicion for adverse drug reaction when evaluating altered mental status in these patients if they are receiving ULTRAM ER (see WARNINGS - Respiratory Depression).

**Use in Ambulatory Patients:** ULTRAM ER may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. The patient using this drug should be cautioned accordingly.

**Use with MAO Inhibitors and Serotonin Re-uptake Inhibitors:** Use ULTRAM ER with great caution in patients taking monoamine oxidase inhibitors. Animal studies have shown increased deaths with combined administration. Concomitant use of ULTRAM ER with MAO inhibitors or SSRIs increases the risk of adverse events, including seizure and serotonin syndrome.

**Withdrawal:** Withdrawal symptoms may occur if ULTRAM ER is discontinued abruptly. These symptoms may include: anxiety, sweating, insomnia, rigors, pain, nausea, tremors, diarrhea, upper respiratory symptoms, piloerection, and rarely hallucinations. Clinical experience suggests that withdrawal symptoms may be reduced by tapering ULTRAM ER.

**Misuse, Abuse and Diversion of Opioids:** Tramadol is an opioid agonist of the morphine type. Such drugs are sought by drug abusers and people with addiction disorders and are subject to criminal diversion. Tramadol can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing ULTRAM ER in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion. ULTRAM ER could be abused by crushing, chewing, snorting, or injecting the dissolved product. These practices will result in the uncontrolled delivery of the opioid and pose a significant risk to the abuser that could result in overdose and death (see WARNINGS and DRUG ABUSE AND ADDICTION). Concerns about abuse, addiction, and diversion should not prevent the proper management of pain. The development of addiction to opioid analgesics in properly managed patients with pain has been reported to be rare. However, data are not available to establish the true incidence of addiction in chronic pain patients. Healthcare professionals should contact their State Professional Licensing Board, or State Controlled Substances Authority for information on how to prevent and detect abuse or diversion of this product.

**Interactions with Alcohol and Drugs of Abuse:** Tramadol may be expected to have additive effects when used in conjunction with alcohol, other opioids, or illicit drugs that cause central nervous system depression.

**DRUG ABUSE AND ADDICTION:** Tramadol has been shown to cross the placenta. The mean ratio of serum tramadol in the umbilical veins compared to maternal veins was 0.83 for 40 women treated with tramadol HCl during labor. The effect of ULTRAM ER, if any, on the later growth, development, and functional maturation of the child is unknown.

**Nursing Mothers:** ULTRAM ER is not recommended for obstetrical preparative medication or for post-delivery analgesia in nursing mothers because its safety in infants and newborns has not been studied. Following a single IV 100-mg dose of tramadol, the cumulative excretion in breast milk within sixteen hours postdose was 100 µg of tramadol (0.1% of the maternal dose) and 27 µg of M1.

**Pediatric Use:** The safety and efficacy of ULTRAM ER in patients under 18 years of age have not been established. The use of ULTRAM ER in the pediatric population is not recommended.

**Geriatric Use:** Nine-hundred-one elderly (65 years of age or older) subjects were exposed to ULTRAM ER in clinical trials. Of those subjects, 156 were 75 years of age and older. In general, higher incidence rates of adverse events were observed for patients older than 65 years of age compared with patients 65 years and younger, particularly for the following adverse events: constipation, fatigue, weakness, postural hypotension and dyspepsia. For this reason, ULTRAM ER should be used with great caution in patients older than 75 years of age (see CLINICAL PHARMACOLOGY in full Prescribing Information and DOSAGE AND ADMINISTRATION).

**ADVERSE REACTIONS:** ULTRAM ER was administered to a total of 3108 patients during studies conducted in the U.S. These included four double-blind studies in patients with osteoarthritis and/or chronic low back pain and one open-label study in patients with chronic non-malignant pain. A total of 901 patients were 65 years or older. Adverse events increased with dose from 100 mg to 400 mg in the two pooled, twelve-week, randomized, double-blind, placebo-controlled studies in patients with chronic non-malignant pain (see Table 1). **Table 1: Incidence (%) of patients with adverse event rates  $\geq$  5% from two 12-week placebo-controlled studies in patients with moderate to moderately severe chronic pain by dose.**

MedDRA Preferred Term first; followed by ULTRAM ER 100 mg (N=403) n (%); second; ULTRAM ER 200 mg (N=400) n (%); third; ULTRAM ER 300 mg (N=400) n (%); fourth; ULTRAM ER 400 mg (N=202) n (%); fifth; and Placebo (N=406) n (%); sixth: Dizziness (not vertigo): 64 (15.9), 81 (20.3), 90 (22.5), 57 (28.2), 28 (6.9); Nausea: 61 (15.1), 90 (22.5), 102 (25.5), 53 (26.2), 32 (7.9); Constipation: 49 (12.2), 68 (17.0), 85 (21.3), 60 (29.7), 17 (4.2); Somnolence: 33 (8.2), 45 (11.3), 29 (7.3), 41 (20.3), 7 (1.7); Flushing: 31 (7.7), 40 (10.0), 35 (8.8), 32 (15.8), 18 (4.4); Pruritus: 25 (6.2), 34 (8.5), 30 (7.5), 24 (11.9), 4 (1.0); Vomiting: 20 (5.0), 29 (7.3), 34 (8.5), 19 (9.4), 11 (2.7); Insomnia: 26 (6.5), 32 (8.0), 36 (9.0), 22 (10.9), 13 (3.2); Asthenia: 14 (3.5), 24 (6.0), 26 (6.5), 13 (6.4), 7 (1.7); Postural hypotension: 7 (1.7), 17 (4.3), 8 (2.0), 11 (5.4), 9 (2.2); Sweating increased: 6 (1.5), 8 (2.0), 15 (3.8), 13 (6.4), 1 (0.2); Weakness: 3 (0.7), 8 (2.0), 14 (3.5), 9 (4.5), 1 (1.2); Rigors: 3 (0.7), 2 (0.5), 9 (2.3), 7 (3.5), 1 (0.2); Anorexia: 3 (0.7), 7 (1.8), 21 (5.3), 12 (5.9), 1 (0.2); Influenza like illness: 1 (0.2), 6 (1.5), 7 (1.8), 4 (2.0), 2 (0.5).

**Adverse events with incidence rates of 1.0% to <5.0%: Eye disorders:** vision blurred; **Gastrointestinal disorders:** abdominal pain upper, dyspepsia, abdominal pain, sore throat; **General disorders:** weakness, pain, feeling hot, influenza like illness, fall, rigors, lethargy, pyrexia, chest pain; **Infections and infestations:** nasopharyngitis, upper respiratory tract infection, sinusitis, influenza, gastroenteritis viral, urinary tract infection, bronchitis; **Investigations:** blood creatine phosphokinase increased; **Metabolism and nutrition disorders:** appetite decreased, weight decreased, anorexia; **Musculoskeletal, connective tissue and bone disorders:** arthralgia, back pain, pain in limb, neck pain; **Nervous system disorders:** tremor, paraesthesia, hypoaesthesia; **Psychiatric disorders:** nervousness, anxiety, depression, restlessness; **Respiratory, thoracic and mediastinal disorders:** rhinorrhea, nasal congestion, dyspnoea, sinus congestion, cough, sneezing; **Skin and subcutaneous tissue disorders:** sweating increased, dermatitis; **Vascular disorders:** postural hypotension, hot flashes, vasodilatation.

**Adverse events with incidence rates <1.0%: Cardiac disorders:** palpitations, myocardial infarction; **Ear and labyrinth disorders:** tinnitus; **Gastrointestinal disorders:** flatulence, constipation aggravated, toothache, pancreatitis; **General disorders:** feeling jittery, oedema lower limb, shivering, joint swelling, malaise, drug withdrawal syndrome, peripheral swelling; **Hepato-biliary disorders:** cholelithiasis, cholecystitis; **Infections and infestations:** appendicitis, cellulitis, ear infection, gastroenteritis, pneumonia, urinary tract infection, viral infection, injury and poisoning; joint strain, muscle injury; **Investigations:** heart rate increased, liver function tests abnormal, blood pressure increased, alanine aminotransferase, aspartate aminotransferase increased, blood glucose increased, weight decreased; **Musculoskeletal, connective tissue and bone disorders:** joint stiffness, myalgia, muscle cramps, muscle spasms, muscle twitching, osteoarthritis aggravated; **Nervous system disorders:** migraine, syncope, disturbance in attention, dizziness aggravated, vertigo, sedation; **Psychiatric disorders:** irritability, libido decreased, euphoric mood, sleep disorder, agitation, disorientation, abnormal dreams; **Renal and urinary disorders:** difficulty in micturition, urinary frequency, urinary retention, dysuria, haematuria; **Respiratory, thoracic and mediastinal disorders:** yawning; **Skin and subcutaneous tissue disorders:** contusion, clamminess, night sweats, urticaria, piloerection; **Vascular disorders:** hypertension aggravated, hypertension, peripheral ischaemia.

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**Potential for Other Drugs to Affect Tramadol:** *In vitro* drug interaction studies in human liver microsomes indicate that concomitant administration with inhibitors of CYP2D6 such as fluoxetine, paroxetine, and amitriptyline could result in some inhibition of the metabolism of tramadol. Administration of CYP3A4 inhibitors, such as ketoconazole and erythromycin, or inducers, such as rifampin and St. John's Wort, with ULTRAM ER may affect the metabolism of tramadol leading to altered tramadol exposure.

**Potential for Tramadol to Affect Other Drugs:** *In vitro* drug interaction studies in human liver microsomes indicate that tramadol has no effect on quinidine metabolism. *In vitro* studies indicate that tramadol unlikely to inhibit the CYP3A4-mediated metabolism of other drugs when administered concomitantly at therapeutic doses. Tramadol is a mild inducer of selected drug metabolism pathways measured in animals.

**CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY:** No carcinogenic effect of tramadol was observed in p53(+/-)-heterozygous mice at oral doses up to 150 mg/kg/day (approximately 2-fold maximum daily human dose [MDHD] of 400 mg/day for a 60 kg adult based on body surface conversion) for 26 weeks and in rats at oral doses up to 75 mg/kg/day for males and 100 mg/kg/day for females (approximately 2-fold MDHD) for two years. However, the excessive decrease in body weight gain observed in the rat study might have reduced their sensitivity to any potential carcinogenic effect of the drug. Tramadol was not mutagenic in the following assays: a bacterial reverse mutation assay using *Salmonella* and *E. coli*, a mouse lymphoma assay (in the absence of metabolic activation), and a bone marrow micronucleus test in mice. Mutagenic results occurred in the presence of metabolic activation in the mouse lymphoma assay. Overall, the weight of evidence from these tests indicates that tramadol does not pose a genotoxic risk to humans. No effects on fertility were observed for tramadol at oral dose levels up to 50 mg/kg/day in male and female rats (approximately equivalent to MDHD).

**Pregnancy: Teratogenic Effects: Pregnancy Category C:** Tramadol was not teratogenic at oral dose levels up to 50 mg/kg/day (approximately equivalent to MDHD) in rats and 100 mg/kg (approximately 5-fold MDHD) in rabbits during organogenesis. However, embryo-fetal lethality, reductions in fetal weight and skeletal ossification, and increased supernumerary ribs were observed at a maternal toxic dose of 140 mg/kg in mice (approximately 2-fold MDHD), 80 mg/kg in rats (2-fold MDHD) or 300 mg/kg in rabbits (approximately 15-fold MDHD).

**Non-teratogenic Effects:** Tramadol caused a reduction in neonatal body weight and survival at an oral dose of 80 mg/kg (approximately 2-fold MDHD) when rats were treated during late gestation throughout lactation period. There are no adequate and well-controlled studies in pregnant women. ULTRAM ER should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Neonatal seizures, neonatal withdrawal syndrome, fetal death and still birth have been reported during post-marketing reports with tramadol HCl immediate-release products.

**Labor and Delivery:** ULTRAM ER should not be used in pregnant women prior to or during labor unless the potential benefits outweigh the risks. Safe use in pregnancy has not been established. Chronic use during pregnancy may lead to physical dependence and post-partum withdrawal symptoms in the newborn (see

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LB0047-02B

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Unit of Ortho-McNeil, Inc.

Rev. 01/06



Those with axial involvement should skip DMARDs and go directly to a biologic agent.

DR. DAVIS

physicians can print out the one-page form and have patients fill it out in their offices. The form is available at [www.spondylitis.org/physician\\_resources/cme/basda.pdf](http://www.spondylitis.org/physician_resources/cme/basda.pdf).

In studies using the ASAS 5/6 Improvement Criteria, patient responses to tumor necrosis factor (TNF) inhibition approached 50%. Under this protocol, said Dr. Davis, patients had to have an improvement of at least 20% in four of five domains, including patient global, pain, function, inflammation, C-reactive protein, and/or spinal mobility. “Also, total spinal fusion is not a contraindication for using anti-TNF agents, as about 10% of patients who enrolled in the adalimumab study could have had total spinal fusion yet they responded to that drug,” he said, stressing that because anti-TNF therapy is lifelong, patients need to understand its risks and benefits.

International guidelines for treating patients with AS have been modified by the Spondyloarthritis Research and Treatment Network (SPARTAN) and are now in print (J. Rheumatol. 2006;33:978-82). “You can use the modified New York criteria or other evidence of spondyloarthropathy including inflammatory back pain, elevated acute phase reactants, rapid radiographic progression, spinal inflammation on imaging—including MRI—or, interestingly, ultrasound,” Dr. Davis explained, noting that French researchers found ultrasound to be especially useful in assessing enthesopathies.

“Your patient should have a BASDAI score of at least 4, and you as a physician should assign a moderate disease activity score on either a visual analog scale or the Likert scale. In general, there are three clinical presentations you need to keep in mind ... the axial, peripheral arthritis excluding the hip, and the entheses. Pick out the predominant feature that you’re going to treat and follow. All the manifestations should be treated with at least two courses of an NSAID, and those with significant

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# AS Effects on Shoulder Often Are Overlooked

BY NANCY WALSH  
New York Bureau

GLASGOW, SCOTLAND — Shoulder involvement is often overlooked in ankylosing spondylitis, despite patients' reports that upper body pain interferes with their daily activities, Dr. Charlotte E. Page reported in a poster session at the annual meeting of the British Society for Rheumatology.

Among a group of 31 ankylosing spondylitis (AS) patients attending a 2-week physiotherapy program who responded to questionnaires about their symptoms, 12 reported current shoulder pain, while 10 patients reported experiencing shoulder pain in the past, reported Dr. Page of the rheumatology department of University Hospital of Wales, Cardiff. The patients, aged 17-62 years, had a mean AS duration of 19 years.

Among patients with current shoulder pain, four reported bilateral symptoms, and nine indicated that their daily activities were affected. Among those with previous pain, three study patients reported that their shoulder involvement continued to interfere with their daily activities, noted Dr. Page.

The reported prevalence of shoulder pain among the general population is approximately 12%, and estimates among those with AS range from 7% to 33%, she noted. "Our prevalence of 39% is slightly higher, probably reflecting the type of patients who attend intensive physiotherapy programs."

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arthritis or refractory enthesopathies should have failed either methotrexate or sulfasalazine at maximally tolerated doses for at least 3 months. For those with axial involvement, there's no requirement for nonbiologic disease-modifying antirheumatic drugs (DMARDs) and they should go directly to a biologic agent," Dr. Davis said, adding that methotrexate and leflunomide have shown little evidence of efficacy in AS, while sulfasalazine has been shown to have effects mostly on peripheral manifestations. "Thalidomide and pamidronate interestingly have weak anti-TNF activity and have shown some clinical efficacy in small trials."

Muscle relaxants can help, particularly when the patient is starting physical therapy. Corticosteroids injected into the sacroiliac joints alleviate refractory pain and topical corticosteroids are effective in treating acute anterior uveitis, Dr. Davis said.

After placing a patient on TNF blockade, expect a response (based on clinical trials and clinical experience) within 12 weeks. "And you want a change in your BASDAI score of at least 50% or two units, and a change in your physician global score of at least one." Etanercept and infliximab have FDA approval, while approval of adalimumab is pending. Patients taking these medications should be screened for tuberculosis and consideration should be given to testing for hepatitis, especially in those from endemic areas, Dr. Davis said. ■

Only 10 of the 22 patients who had either current or past shoulder pain had undergone one or more radiologic investigations. Eight had been evaluated with plain radiographs, three with ultrasound, and three with MRI arthrograms.

Among the eight patients who had received one or more corticosteroid injections to the shoulder region, five reported still having shoulder pain and six reported still experiencing symptoms that interfered with daily activities. Among the

seven who had received physiotherapy directed at their shoulder symptoms, five continued to experience pain.

Specific physiotherapy and corticosteroid injections had therefore been given to only 32% and 36% of patients, respectively, and had not alleviated the symptoms in the majority, she noted.

Moreover, a total of 26 patients reported peripheral joint involvement other than the shoulder. Despite this, only six patients received disease-modifying antirheumatic

drugs or anti-tumor necrosis factor- $\alpha$  therapy, which suggests an underappreciation of the extent of AS patients' peripheral joint pain, according to Dr. Page.

Much of the shoulder involvement was rotator cuff tendonitis, which can be imaged and treated, Dr. Page said in an interview. Patients should be asked specifically about this, she said.

"We all know about their hip pain but we seem to forget about the top half" of the body, she said. ■

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