

Rituximab Effective as First-Line Biologic for RA

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LIVERPOOL, ENGLAND — Rituximab has been used successfully in a real-world setting as a first-line biologic therapy for rheumatoid arthritis that does not respond to conventional disease-modifying drugs, Dr. Ai Lyn Tan reported at the annual meeting of the British Society for Rheumatology.

Rituximab is licensed in the United Kingdom for the treatment of adults with

rheumatoid arthritis (RA) who have had an inadequate response to, or who are intolerant of, conventional disease-modifying anti-rheumatic drugs (DMARDs) and to one or more tumor necrosis factor (TNF) inhibitors. In the United States, it is licensed for use in combination with methotrexate for management of moderately to severely active RA that has not responded to treatment with one or more anti-TNF agents.

Dr. Tan and her colleagues at the University of Leeds (England) and Chapel All-

erton Hospital, Leeds, have studied a total of 39 patients who had failed at least one DMARD and who received two initial infusions of rituximab 2 weeks apart. In 17 patients, the doses were 1,000 mg each, and in 22, the doses were 500 mg each.

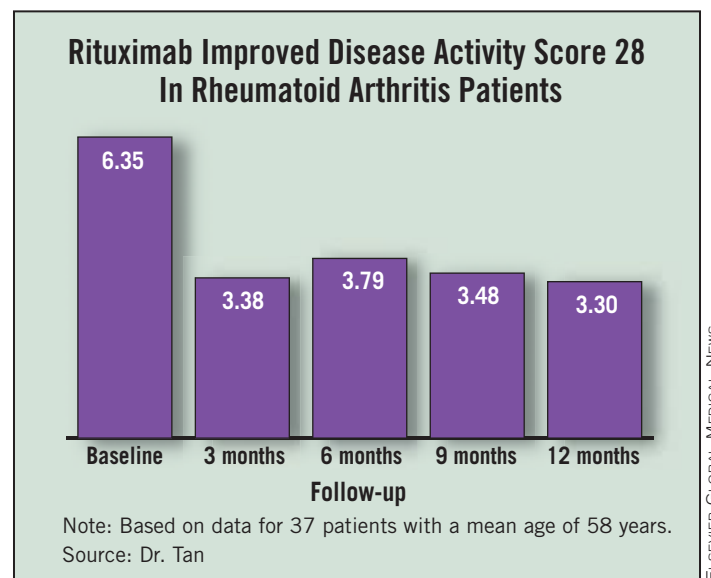
Two-thirds of the patients were women. Their median age was 58 years and median disease duration was 7 years. Thirty were rheumatoid factor (RF) positive at baseline, and 16 were also antinuclear antibody (ANA) positive. Clinical outcome data were available for 37 patients and safety data for all 39.

Clinical assessments using the Disease Activity Score (DAS) 28 and EULAR response criteria were done at 3, 6, 9, and 12 months. The EULAR response criteria use the change in DAS and the level of DAS achieved to classify patients as good, moderate, or nonresponders.

At all time points, there was a significant improvement in DAS28 (see the chart). EULAR good responses were seen in 40% of patients at 3 months and in 50% of patients at 12 months, while overall EULAR responses were seen in 88% and 77%, respectively, at those time points.

By 6 months, ANA became negative in 40% of patients in whom it had been positive at baseline, and in 88% of RF-positive patients the antibody level had fallen. Four of the previously RF-positive patients became seronegative by 6 months, and these reductions were sustained at 12 months, Dr. Tan wrote in a poster presentation.

Slightly better responses were seen in patients who received the higher dose,



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(5% and 4%); Fatigue (5% and 2%). **Psychiatric Disorders:** Insomnia (9% and 4%); Somnolence (6% and 2%); Appetite Decreased (3% and 1%); Libido Decreased (3% and 1%). **Respiratory System Disorders:** Rhinitis (5% and 4%); Sinusitis (3% and 2%). **Urogenital:** Ejaculation Disorder* (9% and <1%); Impotence (3% and <1%); Anorgasmia* (2% and <1%). *Events reported by at least 2% of patients treated with Lexapro are reported, except for the following events which had an incidence on placebo > Lexapro: headache, upper respiratory tract infection, back pain, pharyngitis, inflamed injury, anxiety. *Primarily ejaculatory delay. †Denominator used was for males only (N=225 Lexapro; N=188 placebo). ‡Denominator used was for females only (N=490 Lexapro; N=404 placebo). **Generalized Anxiety Disorder Table 3** enumerates the incidence, rounded to the nearest percent of treatment-emergent adverse events that occurred among 429 GAD patients who received Lexapro 10 to 20 mg/day in placebo-controlled trials. Events included are those occurring in 2% or more of patients treated with Lexapro and for which the incidence in patients treated with Lexapro was greater than the incidence in placebo-treated patients. The most commonly observed adverse events in Lexapro patients (incidence of approximately 5% or greater and approximately twice the incidence in placebo patients) were nausea, ejaculation disorder (primarily ejaculatory delay), insomnia, fatigue, decreased libido, and anorgasmia (see TABLE 3). **TABLE 3. Treatment-Emergent Adverse Events: Incidence in Placebo-Controlled Clinical Trials for Generalized Anxiety Disorder (Percentage of Patients Reporting Event) Body System/Adverse Event (Lexapro (N=429) and Placebo (N=427)).** **Autonomic Nervous System Disorders:** Dry Mouth (9% and 5%); Sweating Increased (4% and 1%). **Central & Peripheral Nervous System Disorders:** Headache (24% and 17%); Paresthesia (2% and 1%). **Gastrointestinal Disorders:** Nausea (18% and 8%); Diarrhea (8% and 6%); Constipation (5% and 4%); Indigestion (3% and 2%); Vomiting (3% and 1%); Abdominal Pain (2% and 1%); Flatulence (2% and 1%); Toothache (2% and 0%). **General:** Fatigue (8% and 2%); Influenza-like symptoms (5% and 4%). **Musculoskeletal:** Neck/Shoulder Pain (3% and 1%). **Psychiatric Disorders:** Somnolence (13% and 7%); Insomnia (12% and 4%); Libido Decreased (7% and 2%); Dreaming Abnormal (3% and 2%); Appetite Decreased (3% and 1%); Lethargy (3% and 1%); Yawning (2% and 1%). **Urogenital:** Ejaculation Disorder* (14% and 2%); Anorgasmia* (6% and <1%); Menstrual Disorder (2% and 1%). *Events reported by at least 2% of patients treated with Lexapro are reported, except for the following events which had an incidence on placebo > Lexapro: inflamed injury, dizziness, back pain, upper respiratory tract infection, rhinitis, pharyngitis. †Primarily ejaculatory delay. ‡Denominator used was for males only (N=182 Lexapro; N=195 placebo). †Denominator used was for females only (N=247 Lexapro; N=232 placebo). **Dose Dependency of Adverse Events** The potential dose dependency of common adverse events (defined as an incidence rate of ≥ 5% in either the 10 mg or 20 mg Lexapro groups) was examined on the basis of the combined incidence of adverse events in two fixed-dose trials. The overall incidence rates of adverse events in 10 mg Lexapro-treated patients (66%) was similar to that of the placebo-treated patients (61%), while the incidence rate in 20 mg/day Lexapro-treated patients was greater (86%). **Table 4** shows common adverse events that occurred in the 20 mg/day Lexapro group with an incidence that was approximately twice that of the 10 mg/day Lexapro group and approximately twice that of the placebo group. **TABLE 4: Incidence of Common Adverse Events* in Patients with Major Depressive Disorder Receiving Placebo (N=311), 10 mg/day Lexapro (N=310), 20 mg/day Lexapro (N=125):** Insomnia (4%, 7%, 14%); Diarrhea (5%, 6%, 14%); Dry Mouth (3%, 4%, 9%); Somnolence (1%, 4%, 9%); Dizziness (2%, 4%, 7%); Sweating Increased (<1%, 3%, 8%); Constipation (1%, 3%, 6%); Fatigue (2%, 2%, 6%); Indigestion (1%, 2%, 6%); *Adverse events with an incidence rate of at least 5% in either the Lexapro groups and with an incidence rate in the 20 mg/day Lexapro group that was approximately twice that of the 10 mg/day Lexapro group and the placebo group. **Male and Female Sexual Dysfunction with SSRIs** Although changes in sexual desire, sexual performance, and sexual satisfaction often occur as manifestations of a psychiatric disorder, they may also be a consequence of pharmacologic treatment. In particular, some evidence suggests that SSRIs can cause such untoward sexual experiences. Reliable estimates of the incidence and severity of untoward experiences involving sexual desire, performance, and satisfaction are difficult to obtain, however, in part because patients and physicians may be reluctant to discuss them. Accordingly, estimates of the incidence of untoward sexual experience and performance cited in product labeling are likely to underestimate their actual incidence. **Table 5** shows the incidence rates of sexual side effects in patients with major depressive disorder and GAD in placebo-controlled trials. **TABLE 5: Incidence of Sexual Side Effects in Placebo-Controlled Clinical Trials (In Males Only: Adverse Event: Lexapro (N=407) and Placebo (N=383)); Ejaculation Disorder (primarily ejaculatory delay) (12% and 1%); Libido Decreased (6% and 2%); Impotence (2% and <1%). (In Females Only: Lexapro (N=737) and Placebo (N=636)); Libido Decreased (3% and 1%); Anorgasmia (3% and <1%).** There are no adequately designed studies examining sexual dysfunction with escitalopram treatment. Priligis has been reported with all SSRIs. While it is difficult to know the precise risk of sexual dysfunction associated with the use of SSRIs, physicians should routinely inquire about such possible side effects. **Vital Sign Changes** Lexapro and placebo groups were compared with respect to (1) mean change from baseline in vital signs (pulse, systolic blood pressure, and diastolic blood pressure) and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses did not reveal any clinically important changes in vital signs associated with Lexapro treatment. In addition, a comparison of supine and standing vital sign measures in subjects receiving Lexapro indicated that Lexapro treatment is not associated with orthostatic changes. **Weight Changes** Patients treated with Lexapro in controlled trials did not differ from placebo-treated patients with regard to clinically important change in body weight. **Laboratory Changes** Lexapro and placebo groups were compared with respect to (1) mean change from baseline in various serum chemistry, hematology, and urinalysis variables, and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses revealed no clinically important changes in laboratory test parameters associated with Lexapro treatment. **ECG Changes** Electrocardiograms from Lexapro (N=625) and placebo (N=571) groups were compared with respect to (1) mean change from baseline in various ECG parameters and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses revealed (1) a decrease in heart rate of 2.2 bpm for Lexapro and 2.7 bpm for placebo, compared to an increase of 0.3 bpm for placebo and (2) an increase in QTc interval of 3.9 msec for Lexapro and 3.7 msec for placebo, compared to 0.5 msec for placebo. Neither Lexapro nor placebo treatment was associated with the development of clinically significant ECG abnormalities. **Other Events Observed During the Premarketing Evaluation of Lexapro** Following is a list of WHO terms that reflect treatment-emergent adverse events, as defined in the introduction to the ADVERSE REACTIONS section, reported by the 1428 patients treated with Lexapro for periods of up to one year in double-blind or open-label clinical trials during its premarketing evaluation. All reported events are included except those already listed in Tables 2 & 3, those occurring in only one patient, event terms that are so general as to be uninformative, and those that are unlikely to be drug related. It is important to emphasize that, although the events reported occurred during treatment with Lexapro, they were not necessarily caused by it. Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring on one or more occasions in at least 1/100 patients; infrequent adverse events are those occurring in less than 1/100 patients but at least 1/1000 patients. **Cardiovascular - Frequent:** palpitation, hypertension. **Infrequent:** bradycardia, tachycardia, ECG abnormal, flushing, varicose vein. **Central and Peripheral Nervous System Disorders - Frequent:** light-headed feeling, migraine. **Infrequent:** tremor, vertigo, restless legs, shaking, twitching, dysequilibrium, tics, carpal tunnel syndrome, muscle contractions involuntary, sluggishness, coordination abnormal, faintness, hyperreflexia, muscular tone increased. **Gastrointestinal Disorders - Frequent:** heartburn, abdominal cramp, gastroenteritis. **Infrequent:** gastroesophageal reflux, bloating, abdominal discomfort, dyspepsia, increased stool frequency, belching, gastritis, hemorrhoids, gagging, polyposis gastric, swallowing difficult. **General - Frequent:** allergy, pain in limb, fever, hot flushes, chest pain. **Infrequent:** edema of extremities, chills, tightness of chest, leg pain, asthenia, syncope, malaise, arachnoiditis, fall. **Hemic and Lymphatic Disorders - Infrequent:** bruise, anemia, nosebleed, hematoma, lymphadenopathy cervical. **Metabolic and Nutritional Disorders - Frequent:** increased weight. **Infrequent:** decreased weight, hyperglycemia, thirst, bilirubin increased, hepatic enzymes increased, gout, hypercholesterolemia. **Musculoskeletal System Disorders - Frequent:** arthralgia, myalgia. **Infrequent:** jaw stiffness, muscle cramp, muscle stiffness, arthritis, muscle weakness, back discomfort, arthropathy, jaw pain, joint stiffness. **Psychiatric Disorders - Frequent:** appetite increased, lethargy, irritability, concentration impaired. **Infrequent:** jitteriness, panic reaction, agitation, apathy, forgetfulness, depression aggravated, nervousness, restlessness aggravated, suicide attempt, amnesia, anxiety attack, bruising, carbohydrate craving, confusion, depersonalization, disorientation, emotional lability, feeling unreal, tremulousness nervous, crying abnormal, depression, excitability, auditory hallucination, suicidal tendency. **Reproductive Disorders/Female* - Frequent:** menstrual cramps, menstrual disorder. **Infrequent:** menorrhagia, breast neoplasm, pelvic inflammation, premenstrual syndrome, spotting between menses. *% based on female subjects only. **N=905 Respiratory System Disorders - Frequent:** bronchitis, sinus congestion, coughing, nasal congestion, sinus headache. **Infrequent:** asthma, breath shortness, laryngitis, pneumonia, tracheitis. **Skin and Appendages Disorders - Frequent:** rash. **Infrequent:** pruritus, acne, alopecia, eczema, dermatitis, dry skin, folliculitis, lipoma, furunculosis, dry lips, skin nodule. **Special Senses - Frequent:** vision blurred, tinnitus. **Infrequent:** taste alteration, earache, conjunctivitis, vision abnormal, dry eyes, eye irritation, visual disturbance, eye infection, pupils dilated, metallic taste. **Urinary System Disorders - Frequent:** urinary frequency, urinary tract infection. **Infrequent:** urinary urgency, kidney stone, dysuria, blood in urine. **Events Reported Subsequent to the Marketing of Escitalopram** - Although no causal relationship to escitalopram treatment has been found, the following adverse events have been reported to have occurred in patients and to be temporally associated with escitalopram treatment during post marketing spontaneous and clinical trial experience and were not observed during the premarketing evaluation of escitalopram: Blood and Lymphatic System Disorders: hemolytic anemia, leukopenia, thrombocytopenia. **Cardiac Disorders:** atrial fibrillation, cardiac failure, myocardial infarction, torsade de pointes, ventricular arrhythmia, ventricular tachycardia. **Endocrine Disorders:** diabetes mellitus, hyperprolactinemia, SIADH. **Eye Disorders:** diplopia, glaucoma. **Gastrointestinal Disorders:** gastrointestinal hemorrhage, pancreatitis, rectal hemorrhage. **General Disorders and Administration Site Conditions:** abnormal gait. **Hepatobiliary Disorders:** fulminant hepatitis, hepatic failure, hepatic necrosis, hepatitis. **Immune System Disorders:** allergic reaction. **Investigations:** electrocardiogram QT prolongation, INR increased, prothrombin decreased. **Metabolism and Nutrition Disorders:** hypoglycemia, hypokalemia. **Musculoskeletal and Connective Tissue Disorders:** rhabdomyolysis. **Nervous System Disorders:** akathisia, choreoathetosis, dysarthria, dyskinesia, dystonia, extrapyramidal disorders, grand mal seizures (or convulsions), hypoaesthesia, myoclonus, neuroleptic malignant syndrome, nystagmus, seizures, serotonin syndrome, tardive dyskinesia. **Pregnancy, Puerperium and Perinatal Conditions:** spontaneous abortion. **Psychiatric Disorders:** acute psychosis, aggression, anger, delirium, delusion, nightmare, paranoia, visual hallucinations. **Renal and Urinary Disorders:** acute renal failure. **Reproductive System and Breast Disorders:** priapism. **Respiratory, Thoracic and Mediastinal Disorders:** pulmonary embolism. **Skin and Subcutaneous Tissue Disorders:** angioedema, ecchymosis, erythema multiforme, photosensitivity reaction, Stevens Johnson Syndrome, toxic epidermal necrolysis, urticaria. **Vascular Disorders:** deep vein thrombosis, hypotension, orthostatic hypotension, phlebitis thrombosis. **Forest Pharmaceuticals, Inc. 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Chest X-Ray Warranted in New RA

LIVERPOOL, ENGLAND — All patients with newly diagnosed rheumatoid arthritis should have a chest x-ray to rule out rare conditions that can cause arthralgias and inflammation.

Dr. Sarah E. Medley based this advice on a case in which a 52-year-old woman with a 45 pack-year history of smoking presented to the orthopedics department of Queen Elizabeth Hospital, Woolwich, England, with arthralgias affecting the knees, shins, and wrists. Although synovial biopsy of the right knee revealed no synovitis, the patient was diagnosed with rheumatoid arthritis (RA) and treated with methotrexate and then sulfasalazine with prednisone and intramuscular corticosteroids. She was subsequently given an additional diagnosis of facet joint arthritis and given tramadol, meloxicam, and gabapentin for pain.

Rheumatoid factor was negative and erythrocyte sedimentation rate rose from 27 to 101 mm/h, while the woman's dis-

ease activity score was very high, at 8.2.

Because conventional treatment was unsuccessful, anti-tumor necrosis factor therapy was planned. Only then was a chest x-ray ordered—as is needed to rule out tuberculosis in patients embarking on biologic therapy. The x-ray revealed a large right apex mass that proved to be a squamous cell carcinoma of the lung. Subsequent resection resulted in rapid and significant improvement in the patient's articular symptoms, and other medications—except analgesics—were stopped because she was receiving adjuvant chemotherapy, Dr. Medley wrote in a poster presented at the annual meeting of the British Society for Rheumatology.

“This case illustrates the need for a chest x-ray in new RA, and emphasizes the fact that atypical unresponsive RA requires review of the diagnosis rather than just treatment escalation,” Dr. Medley wrote.

—Nancy Walsh