

# Post-Rituximab Infection Rates Remain Stable

VITALS

**Major Finding:** Previous treatment with rituximab does not increase infection risk in RA patients who subsequently receive other biologic therapies during the period of peripheral B-cell depletion.

**Data Source:** A subgroup analysis of patients with moderate to severe RA who received rituximab as part of an international clinical trial program.

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BY DIANA MAHONEY

FROM THE ANNUAL MEETING OF THE CANADIAN RHEUMATOLOGY ASSOCIATION

CANCÚN, MEXICO – The use of other biologic therapies in rheumatoid arthritis patients previously treated with rituximab has been shown to not be associated with an increased risk of serious

infection in this population.

“The rate of serious infections [in these patients] is consistent with rates observed in long-term safety analyses of rituximab-treated patients,” reported Dr. Mark C. Genovese.

The study was designed to determine whether residual pharmacodynamic effects following discontinuation of rituximab ren-

der rheumatoid arthritis patients more vulnerable to serious infection during subsequent biologic treatment.

To make that determination, Dr. Genovese, professor of medicine (immunology and rheumatology) at Stanford (Calif.) University, and his colleagues reviewed the outcomes of patients with moderate to severe

not intended to include reactions (1) already listed in previous tables or elsewhere in labeling, (2) for which a drug cause was remote, (3) which were so general as to be uninformative, (4) which were not considered to have significant clinical implications, or (5) which occurred at a rate equal to or less than placebo. Reactions are categorized by body system according to the following definitions: frequent adverse reactions are those occurring in at least 1/100 patients; infrequent adverse reactions are those occurring in 1/100 to 1/1000 patients; rare reactions are those occurring in fewer than 1/1000 patients. **Cardiac Disorders**—Frequent: palpitations; Infrequent: myocardial infarction and tachycardia. **Ear and Labyrinth Disorders**—Frequent: vertigo; Infrequent: ear pain and tinnitus. **Endocrine Disorders**—Infrequent: hypothyroidism. **Eye Disorders**—Frequent: vision blurred; Infrequent: diplopia and visual disturbance. **Gastrointestinal Disorders**—Frequent: flatulence; Infrequent: eructation, gastritis, halitosis, and stomatitis; Rare: gastric ulcer, hematochezia, and melena. **General Disorders and Administration Site Conditions**—Frequent: chills/rigors; Infrequent: feeling abnormal, feeling hot and/or cold, malaise, and thirst; Rare: gait disturbance. **Infections and Infestations**—Infrequent: gastroenteritis and laryngitis. **Investigations**—Frequent: weight increased; Infrequent: blood cholesterol increased. **Metabolism and Nutrition Disorders**—Infrequent: dehydration and hyperlipidemia; Rare: dyslipidemia. **Musculoskeletal and Connective Tissue Disorders**—Frequent: musculoskeletal pain; Infrequent: muscle tightness and muscle twitching. **Nervous System Disorders**—Frequent: dysgeusia, lethargy, and paresthesia/hypoesthesia; Infrequent: disturbance in attention, dyskinesia, myoclonus, and poor quality sleep; Rare: dysarthria. **Psychiatric Disorders**—Frequent: abnormal dreams and sleep disorder; Infrequent: apathy, bruxism, disorientation/confusional state, irritability, mood swings, and suicide attempt; Rare: completed suicide. **Renal and Urinary Disorders**—Infrequent: dysuria, micturition urgency, nocturia, polyuria, and urine odor abnormal. **Reproductive System and Breast Disorders**—Frequent: anorgasmia/orgasm abnormal; Infrequent: menopausal symptoms, and sexual dysfunction. **Respiratory, Thoracic and Mediastinal Disorders**—Frequent: yawning; Infrequent: throat tightness. **Skin and Subcutaneous Tissue Disorders**—Infrequent: cold sweat, dermatitis contact, erythema, increased tendency to bruise, night sweats, and photosensitivity reaction; Rare: ecchymosis. **Vascular Disorders**—Frequent: hot flush; Infrequent: flushing, orthostatic hypotension, and peripheral coldness.

**Postmarketing Spontaneous Reports**—The following adverse reactions have been identified during postapproval use of Cymbalta. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Adverse reactions reported since market introduction that were temporally related to duloxetine therapy and not mentioned elsewhere in labeling include: anaphylactic reaction, aggression and anger (particularly early in treatment or after treatment discontinuation), angioneurotic edema, erythema multiforme, extrapyramidal disorder, galactorrhea, glaucoma, gynecological bleeding, hallucinations, hyperglycemia, hyperprolactinemia, hypersensitivity, hypertensive crisis, muscle spasm, rash, restless legs syndrome, seizures upon treatment discontinuation, supraventricular arrhythmia, tinnitus (upon treatment discontinuation), trismus, and urticaria.

Serious skin reactions including Stevens-Johnson Syndrome that have required drug discontinuation and/or hospitalization have been reported with duloxetine.

**DRUG INTERACTIONS:** Both CYP1A2 and CYP2D6 are responsible for duloxetine metabolism.

**Inhibitors of CYP1A2**—When duloxetine 60 mg was co-administered with fluvoxamine 100 mg, a potent CYP1A2 inhibitor, to male subjects (n=14) duloxetine AUC was increased approximately 6-fold, the  $C_{max}$  was increased about 2.5-fold, and duloxetine  $t_{1/2}$  was increased approximately 3-fold. Other drugs that inhibit CYP1A2 metabolism include cimetidine and quinolone antimicrobials such as ciprofloxacin and enoxacin [see Warnings and Precautions].

**Inhibitors of CYP2D6**—Concomitant use of duloxetine (40 mg once daily) with paroxetine (20 mg once daily) increased the concentration of duloxetine AUC by about 60%, and greater degrees of inhibition are expected with higher doses of paroxetine. Similar effects would be expected with other potent CYP2D6 inhibitors (e.g., fluoxetine, quinidine) [see Warnings and Precautions].

**Dual Inhibition of CYP1A2 and CYP2D6**—Concomitant administration of duloxetine 40 mg twice daily with fluvoxamine 100 mg, a potent CYP1A2 inhibitor, to CYP2D6 poor metabolizer subjects (n=14) resulted in a 6-fold increase in duloxetine AUC and  $C_{max}$ .

**Drugs that Interfere with Hemostasis (e.g., NSAIDs, Aspirin, and Warfarin)**—Serotonin release by platelets plays an important role in hemostasis. Epidemiological studies of the case-control and cohort design that have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding have also shown that concurrent use of an NSAID or aspirin may potentiate this risk of bleeding. Altered anticoagulant effects, including increased bleeding, have been reported when SSRIs or SNRIs are coadministered with warfarin. Patients receiving warfarin therapy should be carefully monitored when duloxetine is initiated or discontinued [see Warnings and Precautions].

**Lorazepam**—Under steady-state conditions for duloxetine (60 mg Q 12 hours) and lorazepam (2 mg Q 12 hours), the pharmacokinetics of duloxetine were not affected by co-administration.

**Temazepam**—Under steady-state conditions for duloxetine (20 mg qhs) and temazepam (30 mg qhs), the pharmacokinetics of duloxetine were not affected by co-administration.

**Drugs that Affect Gastric Acidity**—Cymbalta has an enteric coating that resists dissolution until reaching a segment of the gastrointestinal tract where the pH exceeds 5.5. In extremely acidic conditions, Cymbalta, unprotected by the enteric coating, may undergo hydrolysis to form naphthol. Caution is advised in using Cymbalta in patients with conditions that may slow gastric emptying (e.g., some diabetics). Drugs that raise the gastrointestinal pH may lead to an earlier release of duloxetine. However, co-administration of Cymbalta with

aluminum- and magnesium-containing antacids (51 mEq), or Cymbalta, with famotidine, had no significant effect on the rate or extent of duloxetine absorption after administration of a 40 mg oral dose. It is unknown whether the concomitant administration of proton pump inhibitors affects duloxetine absorption [see Warnings and Precautions].

**Drugs Metabolized by CYP1A2**—*In vitro* drug interaction studies demonstrate that duloxetine does not induce CYP1A2 activity. Therefore, an increase in the metabolism of CYP1A2 substrates (e.g., theophylline, caffeine) resulting from induction is not anticipated, although clinical studies of induction have not been performed. Duloxetine is an inhibitor of the CYP1A2 isoform in *in vitro* studies, and in two clinical studies the average (90% confidence interval) increase in theophylline AUC was 7% (1%-15%) and 20% (13%-27%) when co-administered with duloxetine (60 mg twice daily).

**Drugs Metabolized by CYP2D6**—Duloxetine is a moderate inhibitor of CYP2D6. When duloxetine was administered (at a dose of 60 mg twice daily) in conjunction with a single 50-mg dose of desipramine, a CYP2D6 substrate, the AUC of desipramine increased 3-fold [see Warnings and Precautions].

**Drugs Metabolized by CYP2C9**—Duloxetine does not inhibit the *in vitro* enzyme activity of CYP2C9. Inhibition of the metabolism of CYP2C9 substrates is therefore not anticipated, although clinical studies have not been performed.

**Drugs Metabolized by CYP3A**—Results of *in vitro* studies demonstrate that duloxetine does not inhibit or induce CYP3A activity. Therefore, an increase or decrease in the metabolism of CYP3A substrates (e.g., oral contraceptives and other steroidal agents) resulting from induction or inhibition is not anticipated, although clinical studies have not been performed.

**Drugs Metabolized by CYP2C19**—Results of *in vitro* studies demonstrate that duloxetine does not inhibit CYP2C19 activity at therapeutic concentrations. Inhibition of the metabolism of CYP2C19 substrates is therefore not anticipated, although clinical studies have not been performed.

**Monoamine Oxidase Inhibitors**—[See Contraindications and Warnings and Precautions.] **Switching Patients to or from a Monoamine Oxidase Inhibitor**—At least 14 days should elapse between discontinuation of an MAOI and initiation of therapy with Cymbalta. In addition, at least 5 days should be allowed after stopping Cymbalta before starting an MAOI [see Contraindications and Warnings and Precautions].

**Serotonergic Drugs**—Based on the mechanism of action of SNRIs and SSRIs, including Cymbalta, and the potential for serotonin syndrome, caution is advised when Cymbalta is co-administered with other drugs that may affect the serotonergic neurotransmitter systems, such as triptans, linezolid (an antibiotic which is a reversible non-selective MAOI), lithium, tramadol, or St. John's Wort. The concomitant use of Cymbalta with other SSRIs, SNRIs, or tryptophan is not recommended [see Warnings and Precautions].

**Triptans**—There have been rare postmarketing reports of serotonin syndrome with use of an SSRI and a triptan. If concomitant treatment of Cymbalta with a triptan is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases [see Warnings and Precautions].

**Alcohol**—When Cymbalta and ethanol were administered several hours apart so that peak concentrations of each would coincide, Cymbalta did not increase the impairment of mental and motor skills caused by alcohol. In the Cymbalta clinical trials database, three Cymbalta-treated patients had liver injury as manifested by ALT and total bilirubin elevations, with evidence of obstruction. Substantial intercurrent ethanol use was present in each of these cases, and this may have contributed to the abnormalities seen [see Warnings and Precautions].

**CNS Drugs**—[See Warnings and Precautions.]

**Drugs Highly Bound to Plasma Protein**—Because duloxetine is highly bound to plasma protein, administration of Cymbalta to a patient taking another drug that is highly protein bound may cause increased free concentrations of the other drug, potentially resulting in adverse reactions.

**USE IN SPECIFIC POPULATIONS: Pregnancy—Teratogenic Effects, Pregnancy Category C**—In animal reproduction studies, duloxetine has been shown to have adverse effects on embryo/fetal and postnatal development.

When duloxetine was administered orally to pregnant rats and rabbits during the period of organogenesis, there was no evidence of teratogenicity at doses up to 45 mg/kg/day (7 times the maximum recommended human dose [MRHD, 60 mg/day]) and 4 times the human dose of 120 mg/day on a mg/m<sup>2</sup> basis, in rat; 15 times the MRHD and 7 times the human dose of 120 mg/day on a mg/m<sup>2</sup> basis in rabbit. However, fetal weights were decreased at this dose, with a no-effect dose of 10 mg/kg/day (2 times the MRHD and =1 times the human dose of 120 mg/day on a mg/m<sup>2</sup> basis in rats; 3 times the MRHD and 2 times the human dose of 120 mg/day on a mg/m<sup>2</sup> basis in rabbits).

When duloxetine was administered orally to pregnant rats throughout gestation and lactation, the survival of pups to 1 day postpartum and pup body weights at birth and during the lactation period were decreased at a dose of 30 mg/kg/day (5 times the MRHD and 2 times the human dose of 120 mg/day on a mg/m<sup>2</sup> basis); the no-effect dose was 10 mg/kg/day. Furthermore, behaviors consistent with increased reactivity, such as increased startle response to noise and decreased habituation of locomotor activity, were observed in pups following maternal exposure to 30 mg/kg/day. Post-weaning growth and reproductive performance of the progeny were not affected adversely by maternal duloxetine treatment.

There are no adequate and well-controlled studies in pregnant women; therefore, duloxetine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

**Nonteratogenic Effects**—Neonates exposed to SSRIs or serotonin and norepinephrine reuptake inhibitors (SNRIs), late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. These

RA who received rituximab and methotrexate in an international clinical trial program and who were subsequently treated with a different biologic during the safety follow-up period.

Of the 3,189 RA patients who had received at least one course of rituximab in the clinical trial, 283 were subsequently treated with an alternative biologic agent during safety follow-up, according to Dr. Genovese.

Of these, 230 patients received tumor necrosis factor (TNF) inhibitors as their first subsequent biologic agent after rituximab.

Another 43 received the T-cell inhibitor abatacept (including 2 who subsequently received a TNF inhibitor), 9 received the interleukin-1 inhibitor anakinra (also including 2 who subsequently received a TNF inhibitor), 3 received the interleukin-6 receptor inhibitor tocilizumab, and 2 received experimental biologic agents.



The median time from the last dose of rituximab to the first subsequent biologic was 8 months (mean 10 months), he reported. The average follow-up time after receiving the subsequent biologic was 11 months.

**DR. GENOVESE**

The investigators collected information on “serious infection events,” defined as infections that re-

quired intravenous antibiotics or met the regulatory criteria for a serious adverse event, including infections that required inpatient hospitalization; were immediately life-threatening; were medically significant and required an intervention to prevent one of the previous outcomes; or were fatal.

They calculated the rates of such events for the periods in which patients were on rituximab before the subsequent biologic and after initiation of treatment with the subsequent biologic, Dr. Genovese said.

They also collected peripheral CD19+ counts, which are a surrogate marker for CD20+ B cells.

Following the first dose of rituximab and prior to subsequent biologic therapy, 22 serious infections in 18 patients over 366 patient-years of follow-up (6 events/100 patient-years) were reported. “The infections were variable and typical of RA patients, and did not include any opportunistic or fatal infections,” Dr. Genovese said.

At the time of receiving subsequent biologic treatment, 83% of the patients had peripheral B-cell counts below the lower limit of normal, he noted.

After treatment with another biologic following rituximab, a total of 16 serious infection events – also variable and typical of RA – occurred in 15 patients over 321,64 patient-years of follow-up (5 events/100 patient-years).

The median time to infection after initiating the subsequent biologic was 11 months, he said.

Of the 16 serious infection events, 12 occurred in patients who had received TNF inhibitors as their first post-rituximab biologic, and 4 occurred in patients who had received two biologic drugs post rituximab, said Dr. Genovese.

One serious infection was reported before alternative treatment and one after treatment among the 43 patients who received abatacept, according to Dr. Genovese.

In the subgroup of patients who received a TNF inhibitor following rituximab, the serious infection rates before and after receipt of the drug were 6.03/100 patient-years and 4.51/100 patient-years, respectively.

Overall, the serious infection rates in the 283 patients were statistically similar to the rate of 4.35 events/100 patient-years observed in the all-exposure safety population, according to Dr. Genovese’s presentation.

In the subgroup of patients with CD19+ cell counts of less than 20 cells/mL prior to subsequent biologic treatment, the serious infection rate, found to be at 6 events/100 patient-years, was also consistent with the serious infection rates observed in all patients who were receiving any biologic disease-modifying antirheumatic drug following rituximab, he said.

“The findings answer an important clinical question about the safety of treatment with other biologic drugs during the period of peripheral B-cell depletion in patients who have discontinued rituximab,” Dr. Genovese concluded. ■

features are consistent with either a direct toxic effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome [see *Warnings and Precautions*].

When treating pregnant women with Cymbalta during the third trimester, the physician should carefully consider the potential risks and benefits of treatment. The physician may consider tapering Cymbalta in the third trimester.

Lilly maintains a pregnancy registry to monitor the pregnancy outcomes of women exposed to Cymbalta while pregnant. Healthcare providers are encouraged to register any patient who is exposed to Cymbalta during pregnancy by calling the Cymbalta Pregnancy Registry at 1-866-814-6975 or by visiting [www.cymbaltapregnancyregistry.com](http://www.cymbaltapregnancyregistry.com).

**Labor and Delivery**—The effect of duloxetine on labor and delivery in humans is unknown. Duloxetine should be used during labor and delivery only if the potential benefit justifies the potential risk to the fetus.

**Nursing Mothers**—Duloxetine is excreted into the milk of lactating women. The estimated daily infant dose on a mg/kg basis is approximately 0.14% of the maternal dose. Because the safety of duloxetine in infants is not known, nursing while on Cymbalta is not recommended. However, if the physician determines that the benefit of duloxetine therapy for the mother outweighs any potential risk to the infant, no dosage adjustment is required as lactation did not influence duloxetine pharmacokinetics. (See *Nursing Mothers* section in full PI for additional information.)

**Pediatric Use**—Safety and effectiveness in the pediatric population have not been established [see *Boxed Warning and Warnings and Precautions*]. Anyone considering the use of Cymbalta in a child or adolescent must balance the potential risks with the clinical need.

**Geriatric Use**—Of the 2418 patients in premarketing clinical studies of Cymbalta for MDD, 5.9% (143) were 65 years of age or over. Of the 1041 patients in CLBP premarketing studies, 21.2% (221) were 65 years of age or over. Of the 487 patients in OA premarketing studies, 40.5% (197) were 65 years of age or over. Of the 1074 patients in the DPNP premarketing studies, 33% (357) were 65 years of age or over. Of the 1761 patients in FM premarketing studies, 7.9% (140) were 65 years of age or over. Premarketing clinical studies of GAD did not include sufficient numbers of subjects age 65 or over to determine whether they respond differently from younger subjects. In the MDD, DPNP, FM, OA, and CLBP studies, no overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. SSRIs and SNRIs, including Cymbalta, have been associated with cases of clinically significant hyponatremia in elderly patients, who may be at greater risk for this adverse event [see *Warnings and Precautions*]. (See *Geriatric Use* section in full PI for additional information.)

**Gender**—Duloxetine’s half-life is similar in men and women. Dosage adjustment based on gender is not necessary.

**Smoking Status**—Duloxetine bioavailability (AUC) appears to be reduced by about one-third in smokers. Dosage modifications are not recommended for smokers.

**Race**—No specific pharmacokinetic study was conducted to investigate the effects of race.

**Hepatic Insufficiency**—[See *Warnings and Precautions-Use in Patients with Concomitant Illness*.] (See *Use in Patients with Concomitant Illness-Hepatic Insufficiency* section in full PI for additional information.)

**Severe Renal Impairment**—[See *Warnings and Precautions-Use in Patients with Concomitant Illness*.] (See *Use in Patients with Concomitant Illness-Severe Renal Impairment* section in full PI for additional information.)

**DRUG ABUSE AND DEPENDENCE: Abuse**—In animal studies, duloxetine did not demonstrate barbiturate-like (depressant) abuse potential. While Cymbalta has not been systematically studied in humans for its potential for abuse, there was no indication of drug-seeking behavior in the clinical trials. However, it is not possible to predict on the basis of premarketing experience the extent to which a CNS active drug will be misused, diverted, and/or abused once marketed. Consequently, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse of Cymbalta (e.g., development of tolerance, incrementation of dose, drug-seeking behavior).

**Dependence**—In drug dependence studies, duloxetine did not demonstrate dependence-producing potential in rats.

**OVERDOSAGE: Signs and Symptoms**—In postmarketing experience, fatal outcomes have been reported for acute overdoses, primarily with mixed overdoses, but also with duloxetine only, at doses as low as 1000 mg. Signs and symptoms of overdose (duloxetine alone or with mixed drugs) included somnolence, coma, serotonin syndrome, seizures, syncope, tachycardia, hypotension, hypertension, and vomiting.

**Management of Overdose**—There is no specific antidote to Cymbalta, but if serotonin syndrome ensues, specific treatment (such as with cyproheptadine and/or temperature control) may be considered. In case of acute overdose, treatment should consist of those general measures employed in the management of overdose with any drug. (See *Management of Overdose* section in full PI for additional information.)

**NONCLINICAL TOXICOLOGY: Carcinogenesis, Mutagenesis, and Impairment of Fertility—Carcinogenesis**—Duloxetine was administered in the diet to mice and rats for 2 years. In female mice receiving duloxetine at 140 mg/kg/day (11 times the maximum recommended human dose [MRHD, 60 mg/day] and 6 times the human dose of 120 mg/day on a mg/m<sup>2</sup> basis), there was an increased incidence of hepatocellular adenomas and carcinomas. The no-effect dose was 50 mg/kg/day (4 times the MRHD and 2 times the human dose of 120 mg/day on a mg/m<sup>2</sup> basis). Tumor incidence was not increased in male mice receiving duloxetine at doses up to 100 mg/kg/day (8 times the MRHD and 4 times the human dose of 120 mg/day on a mg/m<sup>2</sup> basis).

In rats, dietary doses of duloxetine up to 27 mg/kg/day in females (4 times the MRHD and 2 times the human dose of 120 mg/day on a mg/m<sup>2</sup> basis) and up to 36 mg/kg/day in males (6 times the MRHD and 3 times the human dose of 120 mg/day on a mg/m<sup>2</sup> basis) did not increase the incidence of tumors.

**Mutagenesis**—Duloxetine was not mutagenic in the *in vitro* bacterial reverse mutation assay (Ames test) and was not clastogenic in an *in vivo* chromosomal aberration test in mouse bone marrow cells. Additionally, duloxetine was not genotoxic in an *in vitro* mammalian forward gene mutation assay in mouse lymphoma cells or in an *in vitro* unscheduled DNA synthesis (UDS) assay in primary rat hepatocytes, and did not induce sister chromatid exchange in Chinese hamster bone marrow *in vivo*.

**Impairment of Fertility**—Duloxetine administered orally to either male or female rats prior to and throughout mating at doses up to 45 mg/kg/day (7 times the maximum recommended human dose of 60 mg/day and 4 times the human dose of 20 mg/day on a mg/m<sup>2</sup> basis) did not alter mating or fertility.

**PATIENT COUNSELING INFORMATION:** See FDA-approved Medication Guide and Patient Counseling Information section of full PI.

Additional information can be found at [www.Cymbalta.com](http://www.Cymbalta.com)

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