

Rapid Rituximab Infusion May Be Practical

VITALS

Major Finding: An accelerated rituximab infusion protocol was safe and well tolerated among patients with rheumatoid arthritis.

Data Source: A 10-patient prospective, open-label study designed to assess the practicality of a rapid-infusion protocol for rituximab in RA patients in a single community setting.

Disclosures: Dr. Faraawi reported that he had no relevant financial disclosures.

BY DIANA MAHONEY

FROM THE ANNUAL MEETING OF THE
CANADIAN RHEUMATOLOGY
ASSOCIATION

CANCUN, MEXICO – An accelerated rituximab infusion for rheumatoid arthritis is safe and well tolerated in the community setting, a study has shown.

Moreover, the rapid infusion pro-

ocol “optimizes resources in busy rheumatology practices,” Dr. Rafat Faraawi said at the meeting.

As a chimeric monoclonal antibody, rituximab (Rituxan) is often associated with infusion toxicities, particularly during the initial 30-120 minutes of the first infusion, said Dr. Faraawi, a rheumatologist at St. Mary’s General Hospital in Kitchener, Ont.

To minimize the potential for infusion-related events, the drug manufacturers recommend that it be infused slowly, over the course of 4-5 hours – a long duration that is highly resource intensive, particularly in this era of intense competition for “chair time” and nursing attention, he said.

Small pilot studies in the oncology setting have shown that rapid ritux-

Important Safety Information About Cymbalta (Cont.)

Warnings and Precautions (Cont.)

- In clinical trials across indications relative to placebo, treatment with Cymbalta was associated with mean increases of 0.5 mm Hg in systolic blood pressure and 0.8 mm Hg in diastolic blood pressure compared to mean decreases of 0.6 mm Hg systolic and 0.4 mm Hg diastolic in placebo-treated patients. There was no significant difference in the frequency of sustained (3 consecutive visits) elevated blood pressure. Blood pressure should be measured prior to initiating treatment and periodically measured throughout treatment.
- Co-administration of Cymbalta with potent CYP1A2 inhibitors or thioridazine should be avoided.
- SSRIs and SNRIs, including Cymbalta, have been associated with cases of clinically significant hyponatremia that appeared to be reversible when Cymbalta was discontinued. Elderly patients may be at greater risk of developing hyponatremia with SSRIs and SNRIs.
- The effect that alterations in gastric motility may have on the stability of the enteric coating of Cymbalta is unknown. As duloxetine is rapidly hydrolyzed in acidic media to naphthol, caution is advised in using Cymbalta in patients with conditions that may slow gastric emptying (e.g., some diabetics).
- Cymbalta should ordinarily not be administered to patients with any hepatic insufficiency or patients with end-stage renal disease (requiring dialysis) or severe renal impairment (creatinine clearance <30 mL/min).
- As observed in DPNP trials, Cymbalta treatment worsens glycemic control in some patients with diabetes. In the extension phases (up to 52 weeks) of the DPNP studies, an increase in HbA_{1c} in both the Cymbalta (0.5%) and the routine care groups (0.2%) was noted.
- Cymbalta is in a class of drugs known to affect urethral resistance. If symptoms of urinary hesitation develop during Cymbalta treatment, this effect may be drug-related. In postmarketing experience, urinary retention has been observed.

Use in Specific Populations

- Pregnancy and Nursing Mothers: Use only if the potential benefit justifies the potential risk to the fetus or child.

Most Common Adverse Events

- The most commonly reported adverse events (≥5% and at least twice placebo) for Cymbalta vs placebo in controlled clinical trials (N=6020 vs 3962) were: nausea (24% vs 8%), dry mouth (13% vs 5%), somnolence* (10% vs 3%), fatigue (10% vs 5%), constipation* (10% vs 4%), dizziness (10% vs 5%), decreased appetite* (8% vs 2%), and increased sweating (7% vs 2%).

* Events for which there was a significant dose-dependent relationship in fixed-dose studies, excluding three MDD studies that did not have a placebo lead-in period or dose titration.

- In placebo-controlled clinical trials, the overall discontinuation rates due to adverse events were: **MDD:** 9% vs 5%; **GAD:** 15% vs 4%; **DPNP:** 13% vs 5%; **FM:** 20% vs 12%; **OA:** 16% vs 6%; **CLBP:** 17% vs 6%.

The common adverse events reported as a reason for discontinuation and considered to be drug related were:

MDD: nausea (1.3% vs 0.5%). **GAD:** nausea (3.7% vs 0.2%), vomiting (1.3% vs 0%), dizziness (1.0% vs 0.2%). **DPNP:** nausea (3.5% vs 0.7%), dizziness (1.2% vs 0.4%), somnolence (1.1% vs 0%). **FM:** nausea (1.9% vs 0.7%), somnolence (1.5% vs 0%), fatigue (1.3% vs 0.2%). **OA:** nausea (2.9% vs 0.8%), asthenia (1.3% vs 0%). **CLBP:** nausea (3.0% vs 0.7%), somnolence (1.0% vs 0%).

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For more safety information, please see Brief Summary of full Prescribing Information, including Boxed Warning, on following pages.

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Cymbalta[®] DELAYED
RELEASE
duloxetine HCl CAPSULES

Lilly

imab infusion protocols of 60-90 minutes can be administered safely without increasing the risk of infusion-related reactions.

To evaluate the practicality, safety, and tolerability of an accelerated-infusion protocol in the rheumatology setting, Dr. Faraawi and his colleagues recruited 10 patients who were prescribed rituximab for their rheumatoid arthritis to participate in the investigation. The protocol comprised two courses of 1,000-mg infusions given 2 weeks apart. The first infusion followed the recommended 225-minute infusion schedule, while

the subsequent infusions were administered over a period of 120 minutes as follows: 100 mg over 0-30 minutes; 200 mg over 30-60 minutes; 300 mg over 60-90 minutes; and 400 mg over 90-120 minutes, he said.

Prior to the infusions, patients were premedicated with 1,000 mg acetaminophen, 50 mg diphenhydramine, and 100 mg intravenous methylprednisolone. Vital signs were recorded at baseline and at 15, 30, 60, 90, and 120 minutes, said Dr. Faraawi.

The mean age and disease duration of the 10 patients was 50.6 years and 11.4

years, and the mean disease activity score at the first rituximab infusion was 5.9, he reported.

At the time of the presentation, a total of 40 infusions had been administered, 30 of which followed the accelerated-infusion protocol, said Dr. Faraawi. "To date, the rapid infusion of rituximab has been well tolerated by all of the patients, with only one mild infusion reaction, which resolved during the infusion," he said. "In that case, the patient had refused premedication before the third infusion and experienced itching in her throat and ears, sore shoulders, and

tremors, all of which resolved following treatment with intravenous diphenhydramine and methylprednisolone and oral acetaminophen." The patient premedicated prior to subsequent infusions and had no further reactions, Dr. Faraawi said.

Based on the positive findings of this small study, "rapid rituximab infusion is a practical option in a community setting," he said.

"All of the patients were satisfied with the short infusion duration, it was safe and well tolerated, and it optimized patient, nurse, and physician time." ■

CYMBALTA (duloxetine hydrochloride) Delayed-Release Capsules

Brief Summary: Consult the package insert for complete prescribing information.

WARNING: SUICIDALITY AND ANTIDEPRESSANT DRUGS

Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of Cymbalta or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Cymbalta is not approved for use in pediatric patients. [See Warnings and Precautions and Use in Specific Populations.]

INDICATIONS AND USAGE: Major Depressive Disorder—Cymbalta is indicated for the acute and maintenance treatment of major depressive disorder (MDD). The efficacy of Cymbalta was established in four short-term trials and one maintenance trial in adults.

Generalized Anxiety Disorder—Cymbalta is indicated for the treatment of generalized anxiety disorder (GAD). The efficacy of Cymbalta was established in three short-term trials and one maintenance trial in adults.

Diabetic Peripheral Neuropathic Pain—Cymbalta is indicated for the management of neuropathic pain (DPNP) associated with diabetic peripheral neuropathy.

Fibromyalgia—Cymbalta is indicated for the management of fibromyalgia (FM).

Chronic Musculoskeletal Pain—Cymbalta is indicated for the management of chronic musculoskeletal pain. This has been established in studies in patients with chronic low back pain (CLBP) and chronic pain due to osteoarthritis.

CONTRAINDICATIONS: Monoamine Oxidase Inhibitors—Concomitant use in patients taking monoamine oxidase inhibitors (MAOIs) is contraindicated due to the risk of serious, sometimes fatal, drug interactions with serotonergic drugs. These interactions may include hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma. These reactions have also been reported in patients who have recently discontinued serotonergic reuptake inhibitors and are then started on an MAOI. Some cases presented with features resembling neuroleptic malignant syndrome [see Warnings and Precautions].

Uncontrolled Narrow-Angle Glaucoma—In clinical trials, Cymbalta use was associated with an increased risk of mydriasis; therefore, its use should be avoided in patients with uncontrolled narrow-angle glaucoma [see Warnings and Precautions].

WARNINGS AND PRECAUTIONS: Clinical Worsening and Suicide Risk—Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. There has been a long-standing concern, however, that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment.

Pooled analyses of short-term, placebo-controlled trials of antidepressant drugs (SSRIs and others) showed that these drugs increase the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults (ages 18-24) with major depressive disorder (MDD) and other psychiatric disorders. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction with antidepressants compared to placebo in adults aged 65 and older.

The pooled analyses of placebo-controlled trials in children and adolescents with MDD, obsessive compulsive disorder (OCD), or other psychiatric disorders included a total of 24 short-term trials of 9 antidepressant drugs in over 4400 patients. The pooled analyses of placebo-controlled trials in adults with MDD or other psychiatric disorders included a total of 295 short-term trials (median duration of 2 months) of 11 antidepressant drugs in over 77,000 patients. There was considerable variation in risk of suicidality among drugs, but a tendency toward an increase in the younger patients for almost all drugs studied. There were differences in absolute risk of suicidality across the different indications, with the highest incidence in MDD. The risk of differences (drug vs placebo), however, were relatively stable within age strata and across indications. These risk differences (drug-placebo difference in the number of cases of suicidality per 1000 patients treated) are provided in Table 1.

Table 1

Age Range	Drug-Placebo Difference in Number of Cases of Suicidality per 1000 Patients Treated
	Increases Compared to Placebo
<18	14 additional cases
18-24	5 additional cases
	Decreases Compared to Placebo
25-64	1 fewer case
≥65	6 fewer cases

No suicides occurred in any of the pediatric trials. There were suicides in the adult trials, but the number was not sufficient to reach any conclusion about drug effect on suicide.

It is unknown whether the suicidality risk extends to longer-term use, i.e., beyond several months. However, there is substantial evidence from placebo-controlled maintenance trials in adults with depression that the use of antidepressants can delay the recurrence of depression.

All patients being treated with antidepressants for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.

The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

If the decision has been made to discontinue treatment, medication should be tapered, as rapidly as is feasible, but with recognition that discontinuation can be associated with certain symptoms [see Warnings and Precautions for descriptions of the risks of discontinuation of Cymbalta].

Families and caregivers of patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to healthcare providers. Such monitoring should include daily observation by families and caregivers. Prescriptions for Cymbalta should be written for the smallest quantity of capsules consistent with good patient management in order to reduce the risk of overdose.

Screening Patients for Bipolar Disorder—A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. It should be noted that Cymbalta (duloxetine) is not approved for use in treating bipolar depression.

Hepatotoxicity—There have been reports of hepatic failure, sometimes fatal, in patients treated with Cymbalta. These cases have presented as hepatitis with abdominal pain, hepatomegaly, and elevation of transaminase levels to more than twenty times the upper limit of normal with or without jaundice, reflecting a mixed or hepatocellular pattern of liver injury. Cymbalta should be discontinued in patients who develop jaundice or other evidence of clinically significant liver dysfunction and should not be resumed unless another cause can be established.

Cases of cholestatic jaundice with minimal elevation of transaminase levels have also been reported. Other postmarketing reports indicate that elevated transaminases, bilirubin, and alkaline phosphatase have occurred in patients with chronic liver disease or cirrhosis.

Cymbalta increased the risk of elevation of serum transaminase levels in development program clinical trials. Liver transaminase elevations resulted in the discontinuation of 0.3% (89/29,435) of Cymbalta-treated patients. In most patients, the median time to detection of the transaminase elevation was about two months. In placebo-controlled trials in any indication, for patients with normal and abnormal baseline ALT values, elevation of ALT >3 times the upper limit of normal occurred in 1.37% (132/9611) of Cymbalta-treated patients compared to 0.49% (35/7182) of placebo-treated patients. In placebo-controlled studies using a fixed-dose design, there was evidence of a dose response relationship for ALT and AST elevation of >3 times the upper limit of normal and >5 times the upper limit of normal, respectively.

Because it is possible that duloxetine and alcohol may interact to cause liver injury or that duloxetine may aggravate pre-existing liver disease, Cymbalta should not be prescribed to patients with substantial alcohol use or evidence of chronic liver disease.

Orthostatic Hypotension and Syncope—Orthostatic hypotension and syncope have been reported with therapeutic doses of duloxetine. Syncope and orthostatic hypotension tend to occur within the first week of therapy but can occur at any time during duloxetine treatment, particularly after dose increases. The risk of blood pressure decreases may be greater in patients taking concomitant medications that induce orthostatic hypotension (such as antihypertensives) or are potent CYP1A2 inhibitors [see Warnings and Precautions and Drug Interactions] and in patients taking duloxetine at doses above 60 mg daily. Consideration should be given to discontinuing duloxetine in patients who experience symptomatic orthostatic hypotension and/or syncope during duloxetine therapy.

Serotonin Syndrome or Neuroleptic Malignant Syndrome (NMS)-like Reactions—The development of a potentially life-threatening serotonin syndrome or Neuroleptic Malignant Syndrome (NMS)-like reactions have been reported with SNRIs and SSRIs alone, including Cymbalta treatment, but particularly with concomitant use of serotonergic drugs (including triptans) with drugs which impair metabolism of serotonin (including MAOIs), or