

# Prednisone Aids Disease Control in Early RA

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The addition of low-dose prednisone to a methotrexate-based, tight-control strategy leads to better outcomes in early rheumatoid arthritis, according to study results reported by Marije F. Bakker, Ph.D.

Compared with patients who received

methotrexate (MTX) with placebo, those receiving MTX with 10 mg/day prednisone had better control of their disease and less erosive damage to their joints, Dr. Bakker said in an interview.

“The existing strategies leave room for improvement, especially for the number of patients who reach remission,” said Dr. Bakker of University Medical Center Utrecht (the Netherlands) in explaining the study’s rationale. “Besides,

it is important to determine which strategy steps are useful in the tight-control treatment strategies. Also, it is important to decide at which moment early in the treatment of [rheumatoid arthritis] medication should be added to the strategy.”

The CAMERA-II (Computer-Assisted Management of Early Rheumatoid Arthritis-II) trial was designed specifically to test the hypothesis that the addition of prednisone to a tight-control

strategy of early RA using disease-modifying antirheumatic drugs would result in better disease control.

In the randomized, double-blind, placebo-controlled trial, 117 patients received MTX plus prednisone and 119 received MTX with placebo. All patients had early RA, with an onset less than 1 year before enrollment. Patients were at least 18 years old and had no previous DMARD therapy.

## Important Safety Information About Cymbalta

**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.**

### Contraindications

- 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 serotonin reuptake inhibitors and are then started on an MAOI. Some cases presented with features resembling neuroleptic malignant syndrome.

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.

- Cymbalta was associated with an increased risk of mydriasis; therefore, it should not be used in patients with uncontrolled narrow-angle glaucoma and used cautiously in patients with controlled narrow-angle glaucoma.

### Warnings and Precautions

#### • Clinical Worsening and Suicide Risk

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 within the first few months of treatment and when changing the dose. Consider changing the

therapeutic regimen, including possibly discontinuing the medication in patients whose depression is persistently worse or includes symptoms of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, mania, or suicidality that are severe, abrupt in onset, or were not part of the patient’s presenting symptoms. If discontinuing treatment, the medication should be tapered.

**Families and caregivers of patients being treated with antidepressants for any indication should be alerted about the need to monitor patients. 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.**

- Hepatic failure, sometimes fatal, has been reported in patients treated with Cymbalta. 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.
- Because it is possible that Cymbalta and alcohol may interact to cause liver injury or that Cymbalta 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 have been reported with therapeutic doses of Cymbalta. This tends to occur within the first week of therapy but can occur at any time during Cymbalta treatment, particularly after dose increases. Consideration should be given to discontinuing Cymbalta in patients who experience symptomatic orthostatic hypotension and/or syncope.
- 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 with antipsychotics or other dopamine antagonists. Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). Serotonin syndrome, in its most severe form can resemble neuroleptic malignant syndrome, which includes hyperthermia, muscle rigidity, autonomic instability (cont.)

Patients were excluded from the trial if they had major comorbidities such as malignancies or severe diabetes mellitus; abnormal liver or kidney function; leukopenia or thrombocytopenia; evidence of drug or alcohol abuse; treatment with cytotoxic or immunosuppressive drugs within 3 months of the study; or osteoporotic vertebral fractures.

The investigators tailored the MTX treatment to each patient with the goal of achieving remission. If patients did not achieve remission with the maximum tolerable oral MTX dose, investi-

gators first switched the patient to subcutaneous MTX and then added adali-



**Time to sustained remission was 6 months in the experimental group and 11 months in the control group.**

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mumab to the regimen.

After 2 years, patients in the MTX

plus prednisone group had significantly less radiographically confirmed erosive joint damage, as measured by their Sharp/van der Heijde scores. Patients on the MTX with prednisone regimen had significantly lower scores on the DAS28 (Disease Activity Score using a 28-joint count) questionnaire, and lower disability scores on the HAQ (Health Assessment Questionnaire).

A significantly lower proportion of patients in the experimental group required biologic treatment, compared with those on placebo (14% vs. 36%). The time to sustained remission was 6

months in the experimental group and 11 months in the control group, a significant difference. In addition, patients in the experimental group appeared to be somewhat more likely to achieve sustained remission, although this result did not achieve statistical significance (72% vs. 61%;  $P = .09$ ).

Rates of adverse events were similar (29% in the MTX-prednisone group and 35% in the MTX-placebo group).

The trial was supported by the University Medical Center Utrecht and by Abbott. Dr. Bakker stated that she had no relevant financial disclosures. ■

## Important Safety Information About Cymbalta (Cont.)

### Warnings and Precautions (Cont.)

- rapid fluctuation of vital signs, and mental status changes. Patients should be monitored for the emergence of serotonin syndrome or NMS-like signs and symptoms. Concomitant use with serotonin precursors (e.g., tryptophan) is not recommended. Treatment with duloxetine and any concomitant serotonergic or antidopaminergic agents, including antipsychotics, should be discontinued immediately if the above events occur and supportive symptomatic treatment should be initiated.
- SSRIs and SNRIs, including Cymbalta, may increase the risk of bleeding events. Patients should be cautioned about the risk of bleeding associated with concomitant use of Cymbalta and NSAIDs, aspirin, warfarin, or other drugs that affect coagulation.
  - On abrupt or tapered discontinuation, spontaneous reports of adverse events, some of which may be serious, have been reported during the marketing of SSRIs and SNRIs. A gradual reduction in dose rather than abrupt cessation is recommended when possible.
  - Cymbalta should be used cautiously in patients with a history of mania or with a history of a seizure disorder.
  - 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<sub>1c</sub> 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 ( $\geq 5\%$  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%).

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

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