

# Infliximab Reduces RF Titers, but Doesn’t Affect Anti-CCP

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BUDAPEST, HUNGARY — While infliximab therapy for the treatment of rheumatoid arthritis lowers rheumatoid factor titers, the biologic appears to have little effect on another increasingly relevant marker of disease activity: anticyclic citrullinated peptide antibodies, Nathalie Bardin, M.D., said at the 4th International Congress on Autoimmunity. “The long-term effect of infliximab ther-

apy leads to a reduction in rheumatoid factor titers and the induction of IgG anti–double-stranded DNA [anti-dsDNA].” Yet there was no change in anticyclic citrullinated peptide (anti-CCP) levels,” said Dr. Bardin of Hôpital de la Conception, Marseille, France. In a study of 33 rheumatoid arthritis (RA) patients, 20 treated with infliximab (Remicade), 13 untreated, and 20 controls with undetermined arthritis, the researchers measured levels of anti-CCP, anti-dsDNA antibodies, and IgM rheumatoid factor (RF).

Anti-CCP antibodies were identified in 70% of RA patients, regardless of treatment, but only 10% of those with undetermined arthritis. RF was found in 60% of RA patients but only 10% of the controls. The frequency of RF was 55% in treated patients compared with 69% in untreated patients. Dr. Bardin also followed 16 RA patients over 2 years of infliximab therapy. No change in anti-CCP level was found, but there was a drop in RF titers, she said. “IgG anti-dsDNA was only detected in patients treated with infliximab.”

Because of its high specificity and sensitivity, anti-CCP antibody testing is increasingly seen as an important marker of disease activity in RA patients. In a study of 54 patients with early RA, 35 patients with established RA, 33 healthy donors, and 76 patients with non-RA autoimmune diseases, researchers at the University of Florence (Italy) confirmed that the presence of anti-CCP antibodies is specific to the diagnosis of RA and is also an indicator of bone lesions (Autoimmunity 2004;37:495-501). ■



**MOBIC® (meloxicam) Tablets 7.5 mg and 15 mg**  
**Brief Summary of Prescribing Information**  
**INDICATIONS AND USAGE**

MOBIC is indicated for relief of the signs and symptoms of osteoarthritis and rheumatoid arthritis.

**CONTRAINDICATIONS**

MOBIC is contraindicated in patients with known hypersensitivity to meloxicam. It should not be given to patients who have experienced asthma, urticaria, or allergic-type reactions after taking aspirin or other NSAIDs. Severe, rarely fatal, anaphylactoid-like reactions to NSAIDs have been reported in such patients (see WARNINGS, Anaphylactoid Reactions, and PRECAUTIONS, Pre-existing Asthma).

**WARNINGS**

**Gastrointestinal (GI) Effects - Risk of GI Ulceration, Bleeding, and Perforation:**

Serious gastrointestinal toxicity, such as inflammation, bleeding, ulceration, and perforation of the stomach, small intestine or large intestine, can occur at any time, with or without warning symptoms, in patients treated with nonsteroidal anti-inflammatory drugs (NSAIDs). Minor upper gastrointestinal problems, such as dyspepsia, are common and may also occur at any time during NSAID therapy. Therefore, physicians and patients should remain alert for ulceration and bleeding, even in the absence of previous GI symptoms. Patients should be informed about the signs and/or symptoms of serious GI toxicity and the steps to take if they occur. The utility of periodic laboratory monitoring has not been demonstrated, nor has it been adequately assessed. Only one in five patients who develop a serious upper GI adverse event on NSAID therapy is symptomatic. It has been demonstrated that upper GI ulcers, gross bleeding or perforation, caused by NSAIDs, appear to occur in approximately 1% of the patients treated for 3-6 months, and in about 2-4% of patients treated for one year. These trends continue thus, increasing the likelihood of developing a serious GI event at some time during the course of therapy. However, even short-term therapy is not without risk.

NSAIDs should be prescribed with extreme caution in those with a prior history of ulcer disease or gastrointestinal bleeding. Most spontaneous reports of fatal GI events are in elderly or debilitated patients and therefore special care should be taken in treating this population. **To minimize the potential risk for an adverse GI event, the lowest effective dose should be used for the shortest possible duration.** For high-risk patients, alternate therapies that do not involve NSAIDs should be considered.

Studies have shown that patients with a *prior history of peptic ulcer disease and/or gastrointestinal bleeding* and who use NSAIDs, have a greater than 10-fold risk for developing a GI bleed than patients with neither of these risk factors. In addition to a past history of ulcer disease, pharmacoepidemiological studies have identified several other co-therapies or co-morbid conditions that may increase the risk for GI bleeding such as: treatment with oral corticosteroids, treatment with anticoagulants, longer duration of NSAID therapy, smoking, alcoholism, older age, and poor general health status.

**Anaphylactoid Reactions**

Anaphylactoid reactions have occurred in patients without known prior exposure to MOBIC. MOBIC should not be given to patients with the aspirin triad. This symptom complex typically occurs in asthmatic patients who experience rhinitis with or without nasal polyps, or who exhibit severe, potentially fatal bronchospasm after taking aspirin or other NSAIDs (see CONTRAINDICATIONS and PRECAUTIONS, Pre-existing Asthma). Emergency help should be sought in cases where an anaphylactoid reaction occurs.

**Advanced Renal Disease**

In cases with advanced kidney disease, treatment with MOBIC is not recommended. If NSAID therapy must be initiated, close monitoring of the patient's kidney function is advisable (see PRECAUTIONS, Renal Effects).

**Pregnancy**

MOBIC should be avoided in late pregnancy because it may cause premature closure of the ductus arteriosus.

**PRECAUTIONS**

**General**

MOBIC cannot be expected to substitute for corticosteroids or to treat corticosteroid insufficiency. Abrupt discontinuation of corticosteroids may lead to disease exacerbation. Patients on prolonged corticosteroid therapy should have their therapy tapered slowly if a decision is made to discontinue corticosteroids.

The pharmacological activity of MOBIC in reducing inflammation and possibly fever may diminish the utility of these diagnostic signs in detecting complications of presumed noninfectious, painful conditions.

**Hepatic Effects**

Borderline elevations of one or more liver tests may occur in up to 15% of patients taking MOBIC. These laboratory abnormalities may progress, may remain unchanged, or may be transient with continuing therapy. Notable elevations of ALT or AST (approximately three or more times the upper limit of normal) have been reported in approximately 1% of patients in clinical trials with NSAIDs. In addition, rare cases of severe hepatic reactions, including jaundice and fatal fulminant hepatitis, liver necrosis and hepatic failure, some of them with fatal outcomes, have been reported with NSAIDs.

Patients with signs and/or symptoms suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of a more severe hepatic reaction while on therapy with MOBIC. If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), MOBIC should be discontinued.

**Renal Effects**

Caution should be used when initiating treatment with MOBIC in patients with considerable dehydration. It is advisable to rehydrate patients first and then start therapy with MOBIC. Caution is also recommended in patients with pre-existing kidney disease (see WARNINGS, Advanced Renal Disease).

Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal medullary changes. Renal toxicity has also been seen in patients in whom renal prostaglandins have a compensatory role in the maintenance of renal perfusion. In these patients, administration of NSAIDs may cause dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics and ACE inhibitors, and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pretreatment state.

The extent to which metabolites may accumulate in patients with renal failure has not been studied with MOBIC. Because some MOBIC metabolites are excreted by the kidney, patients with significantly impaired renal function should be more closely monitored.

**Hematological Effects**

Anemia is sometimes seen in patients receiving MOBIC. This may be due to fluid retention, GI blood loss, or an incompletely described effect upon erythropoiesis. Patients on long-term treatment with MOBIC should have their hemoglobin or hematocrit checked if they exhibit any signs or symptoms of anemia.

Drugs which inhibit the biosynthesis of prostaglandins may interfere to some extent with platelet function and vascular responses to bleeding.

NSAIDs inhibit platelet aggregation and have been shown to prolong bleeding time in some patients. Unlike aspirin their effect on platelet function is quantitatively less, or of shorter duration, and reversible. MOBIC does not generally affect platelet counts, prothrombin time (PT), or partial thromboplastin time (PTT). Patients receiving MOBIC who may be adversely affected by alterations in platelet function, such as those with coagulation disorders or patients receiving anticoagulants, should be carefully monitored.

**Fluid Retention and Edema**

Fluid retention and edema have been observed in some patients taking MOBIC. Therefore, MOBIC should be used with caution in patients with fluid retention, hypertension, or heart failure.

**Pre-existing Asthma**

Patients with asthma may have aspirin-sensitive asthma. The use of aspirin in patients with aspirin-sensitive asthma has been associated with severe bronchospasm which can be fatal. Since cross reactivity, including bronchospasm, between aspirin and other nonsteroidal anti-inflammatory drugs has been reported in such aspirin-sensitive patients, MOBIC should not be administered to patients with this form of aspirin sensitivity and should be used with caution in patients with pre-existing asthma.

**Information for Patients**

MOBIC can cause discomfort and, rarely, more serious side effects, such as gastrointestinal bleeding, which may result in hospitalization and even fatal outcomes. Although serious GI tract ulcerations and bleeding can occur without warning symptoms, patients should be alert for the signs and symptoms of ulcerations and bleeding, and should ask for medical advice when observing any indicative signs or symptoms. Patients should be made aware of the importance of this follow-up (see WARNINGS, Gastrointestinal (GI) Effects - Risk of GI Ulceration, Bleeding and Perforation).

Patients should report to their physicians signs or symptoms of gastrointestinal ulceration or bleeding, skin rash, weight gain, or edema.

Patients should be informed of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, pruritus, jaundice, right upper quadrant tenderness, and “flu-like” symptoms). If these occur, patients should be instructed to stop therapy and seek immediate medical therapy.

Patients should also be instructed to seek immediate emergency help in the case of an anaphylactoid reaction (see WARNINGS, Anaphylactoid Reactions).

MOBIC should be avoided in late pregnancy because it may cause premature closure of the ductus arteriosus.

**Laboratory Tests**

Patients on long-term treatment with MOBIC should have their CBC and a chemistry profile checked periodically. If clinical signs and symptoms consistent with liver or renal disease develop, systemic manifestations occur (e.g., eosinophilia, rash, etc.) or if abnormal liver tests persist or worsen, MOBIC should be discontinued.

**Drug Interactions**

**ACE Inhibitors**

Reports suggest that NSAIDs may diminish the antihypertensive effect of angiotensin-converting enzyme (ACE) inhibitors. This interaction should be given consideration in patients taking NSAIDs concomitantly with ACE inhibitors.

**Aspirin**

Concomitant administration of aspirin (1000 mg TID) to healthy volunteers tended to increase the AUC (10%) and C<sub>max</sub> (24%) of meloxicam. The clinical significance of this interaction is not known; however, concomitant administration of meloxicam and aspirin is not generally recommended because of the potential for increased adverse effects. Concomitant administration of low-dose aspirin with MOBIC may result in an increased rate of GI ulceration or other complications, compared to use of MOBIC alone. MOBIC is not a substitute for aspirin for cardiovascular prophylaxis.

**Cholestyramine**

Pretreatment for four days with cholestyramine significantly increased the clearance of meloxicam by 50%. This resulted in a decrease in t<sub>1/2</sub>, from 19.2 hours to 12.5 hours, and a 35% reduction in AUC. This suggests the existence of a recirculation pathway for meloxicam in the gastrointestinal tract. The clinical relevance of this interaction has not been established.

**Cimetidine**

Concomitant administration of 200 mg cimetidine QID did not alter the single-dose pharmacokinetics of 30 mg meloxicam.

**Digoxin**

Meloxicam 15 mg once daily for 7 days did not alter the plasma concentration profile of digoxin after 8-acetyldigoxin administration for 7 days at clinical doses. *In vitro* testing found no protein binding drug interaction between digoxin and meloxicam.

**Furosemide**

Clinical studies, as well as post-marketing observations, have shown that NSAIDs can reduce the natriuretic effect of furosemide and thiazide diuretics in some patients. This effect has been attributed to inhibition of renal prostaglandin synthesis. Studies with furosemide agents and meloxicam have not demonstrated a reduction in natriuretic effect. Furosemide single and multiple dose pharmacodynamics and pharmacokinetics are not affected by multiple doses of meloxicam. Nevertheless, during concomitant therapy with furosemide and MOBIC, patients should be observed closely for signs of declining renal function (see PRECAUTIONS, Renal Effects), as well as to assure diuretic efficacy.

**Lithium**

In a study conducted in healthy subjects, mean pre-dose lithium concentration and AUC were increased by 21% in subjects receiving lithium doses ranging from 804 to 1072 mg BID with meloxicam 15 mg QD as compared to subjects receiving lithium alone. These effects have been attributed to inhibition of renal prostaglandin synthesis by MOBIC. Patients on lithium treatment should be closely monitored when MOBIC is introduced, adjusted, or withdrawn.

**Methotrexate**

A study in 13 rheumatoid arthritis (RA) patients evaluated the effects of multiple doses of meloxicam on the pharmacokinetics of methotrexate taken once weekly. Meloxicam did not have a significant effect on the pharmacokinetics of single doses of methotrexate. *In vitro*, methotrexate did not displace meloxicam from its human serum binding sites.

**Warfarin**

Anticoagulant activity should be monitored, particularly in the first few days after initiating or changing MOBIC therapy in patients receiving warfarin or similar agents, since these patients are at an increased risk of bleeding. The effect of meloxicam on the anticoagulant effect of warfarin was studied in a group of healthy subjects receiving daily doses of warfarin that produced an INR (International Normalized Ratio) between 1.2 and 1.8. In these subjects, meloxicam did not alter warfarin pharmacokinetics and the average anticoagulant effect of warfarin as determined by prothrombin time. However, one subject showed an increase in INR from 1.5 to 2.1. Caution should be used when administering MOBIC with warfarin since patients on warfarin may experience changes in INR and an increased risk of bleeding complications when a new medication is introduced.