# NFD May Respond to Thalidomide

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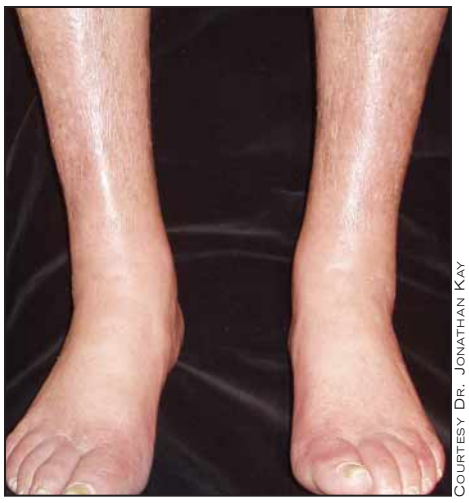
BOSTON — Thalidomide appears promising for the treatment of nephrogenic fibrosing dermopathy, according to the results of a small, open-label trial.

If larger trials show thalidomide to be more effective than placebo or other therapies, patients who have the intractable condition with few treatment options will need to weigh its benefits against associated risks, which include an increased incidence of fetal abnormalities if taken during pregnancy, Stevens-Johnson syndrome, hypotension, and peripheral neuropathy. Side effects of thalidomide include fatigue and drowsiness.

Jonathan Kay, M.D., and colleagues at Massachusetts General Hospital in Boston treated nine men and women with chronic renal failure and a diagnosis of nephrogenic fibrosing dermopathy (NFD) confirmed by biopsy. All patients in the off-label trial received 50 mg of thalidomide daily. Duration of therapy was from 18 days to more than 13 months.

Overall, "the majority of patients experienced improvement in the hardness and tethering of their skin; some also experienced improvement in their joint contractures," Dr. Kay said at a meeting on rheumatology sponsored by Harvard Medical School. ■



COURTESY DR. JONATHAN KAY

**NFD typically involves hyperpigmentation and tethered, thickened skin, as shown on the lower legs of this patient.**

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 $t_{1/2}$, 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 β-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 thiazides in some patients. This response 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 MOBIC, patients should be observed closely for signs of declining renal failure (see **WARNINGS, 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 for signs of lithium toxicity when MOBIC is introduced, adjusted, or withdrawn.

***Methotrexate***

NSAIDs have been reported to competitively inhibit methotrexate accumulation in rabbit kidney slices. This may indicate that they could enhance the toxicity of methotrexate. Caution should be used when NSAIDs are administered concomitantly with 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***

The effects of warfarin and NSAIDs on GI bleeding are synergistic, such that users of both drugs together have a risk of serious GI bleeding higher than users of either drug alone.

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.

**Carcinogenesis, Mutagenesis, Impairment of Fertility**

No carcinogenic effect of meloxicam was observed in rats given oral doses up to 0.8 mg/kg/day (approximately 0.4-fold the human dose at 15 mg/day for a 50 kg adult based on body surface area conversion) for 104 weeks or in mice given oral doses up to 8.0 mg/kg/day (approximately 2.2-fold the human dose, as noted above) for 99 weeks.

Meloxicam was not mutagenic in an Ames assay, or clastogenic in a chromosome aberration assay with human lymphocytes and an *in vivo* micronucleus test in mouse bone marrow.

Meloxicam did not impair male and female fertility in rats at oral doses up to 9 and 5 mg/kg/day, respectively (4.9-fold and 2.5-fold the human dose, as noted above). However, an increased incidence of embryolethality at oral doses ≥ 1 mg/kg/day (0.5-fold the human dose, as noted above) was observed in rats when dams were given meloxicam 2 weeks prior to mating and during early embryonic development.

**Pregnancy**

***Teratogenic Effects:*** *Pregnancy Category C.*

Meloxicam caused an increased incidence of septal defect of the heart, a rare event, at an oral dose of 60 mg/kg/day (64.5-fold the human dose at 15 mg/day for a 50 kg adult based on body surface area conversion) and embryolethality at oral doses ≥ 5 mg/kg/day (5.4-fold the human dose, as noted above) when rabbits were treated throughout organogenesis. Meloxicam was not teratogenic in rats up to an oral dose of 4 mg/kg/day (approximately 2.2-fold the human dose, as noted above) throughout organogenesis. An increased incidence of stillbirths was observed when rats were given oral doses ≥ 1 mg/kg/day throughout organogenesis. Meloxicam crosses the placental barrier. There are no adequate and well-controlled studies in pregnant women. MOBIC should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

***Nonteratogenic Effects***

Because of the known effects of nonsteroidal anti-inflammatory drugs on the fetal cardiovascular system (closure of ductus arteriosus), use during pregnancy (particularly late pregnancy) should be avoided.

Meloxicam caused a reduction in birth index, live births, and neonatal survival at oral doses ≥ 0.125 mg/kg/day (approximately 0.07-fold the human dose at 15 mg/day for a 50 kg adult based on body surface area conversion) when rats were treated during the late gestation and lactation period. No studies have been conducted to evaluate the effect of meloxicam on the closure of the ductus arteriosus in humans; use of meloxicam during the third trimester of pregnancy should be avoided.

**Labor and Delivery**

Studies in rats with meloxicam, as with other drugs known to inhibit prostaglandin synthesis, showed an increased incidence of stillbirths, prolonged delivery, and delayed parturition at oral dosages ≥ 1 mg/kg/day (approximately 0.5-fold the human dose at 15 mg/day for a 50 kg adult based on body surface area conversion), and decreased pup survival at an oral dose of 4 mg/kg/day (approximately 2.1-fold the human dose, as noted above) throughout organogenesis. Similar findings were observed in rats receiving oral dosages ≥ 0.125 mg/kg/day (approximately 0.07-fold the human dose, as noted above) during late gestation and the lactation period.

The effects of MOBIC on labor and delivery in pregnant women are unknown.

**Nursing Mothers**

It is not known whether this drug is excreted in human milk however, meloxicam was excreted in the milk of lactating rats at concentrations higher than those in plasma. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from MOBIC, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

**Pediatric Use**

The safety and effectiveness of meloxicam in pediatric JRA patients from 2 to 17 years of age has been evaluated in three clinical trials (see **CLINICAL TRIALS**, **ADVERSE REACTIONS** and **DOSAGE AND ADMINISTRATION** sections).

**Geriatric Use**

As with any NSAID, caution should be exercised in treating the elderly (65 years and older).

**ADVERSE REACTIONS**

**Adults**

*Osteoarthritis and Rheumatoid Arthritis*

The MOBIC Phase 2/3 clinical trial database includes 10,122 OA patients and 1012 RA patients treated with MOBIC 7.5 mg/day, 3,505 OA patients and 1351 RA patients treated with MOBIC 15 mg/day. MOBIC at these doses was administered to 661 patients for at least 6 months and to 312 patients for at least one year. Approximately 10,500 of these patients were treated in ten placebo and/or active-controlled osteoarthritis trials and 2363 of these patients were treated in ten placebo and/or active-controlled rheumatoid arthritis trials. Gastrointestinal (GI) adverse events were the most frequently reported adverse events in all treatment groups across MOBIC trials.

A 12-week multicenter, double-blind, randomized trial was conducted in patients with osteoarthritis of the knee or hip to compare the efficacy and safety of MOBIC with placebo and with an active control. Two 12-week multicenter, double-blind, randomized trials were conducted in patients with rheumatoid arthritis to compare the efficacy and safety of MOBIC with placebo.

**The following adverse events (%) occurred in ≥ 2% of MOBIC 7.5 mg daily (n=154) and 15 mg daily (n=156) patients, respectively, in a 12-week osteoarthritis placebo- and active-controlled trial:** abdominal pain, 1.9%, 2.6%; diarrhea, 7.8%, 3.2%; dyspepsia, 4.5%, 4.5%; flatulence, 3.2%, 3.2%; nausea, 3.9%, 3.8%; accident household, 4.5%, 3.2%; edema[1], 1.9%, 4.5%; fall, 2.6%, 0.0%; influenza-like symptoms, 4.5%, 5.8%; dizziness, 2.6%, 3.8%; headache, 7.8%, 8.3%; pharyngitis, 0.6%, 3.2%; upper respiratory tract infection, 3.2%, 1.9%; rash[2], 2.6%, 0.6%.

**The following adverse events (%) occurred with MOBIC 7.5 mg daily in ≥2% of patients treated, respectively, in short-term (4-6 weeks) and long-term (6 months) active-controlled osteoarthritis trials:** abdominal pain, 2.7%, 4.7%; constipation, 0.8%, 1.8%; diarrhea, 1.9%, 5.9%; dyspepsia, 3.8%, 8.9%; flatulence, 0.5%, 3.0%; nausea, 2.4%, 4.7%; vomiting, 0.6%, 1.8%; edema[1], 0.6%, 2.4%; pain, 0.9%, 3.6%; dizziness, 1.1%, 2.4%; headache, 2.4%, 3.6%; anemia, 0.1%, 4.1%; arthralgia, 0.5%, 5.3%; back pain, 0.5%, 3.0%; insomnia, 0.4%, 3.6%; coughing, 0.2%, 2.4%; upper respiratory tract infection, 0.2%, 8.3%; pruritus, 0.4%, 2.4%; rash[2], 0.3%, 3.0%; micturition frequency, 0.1%, 2.4%; urinary tract infection, 0.3%, 4.7%.

**The following adverse events (%) occurred with MOBIC 15 mg daily in ≥2% of patients treated, respectively, in short-term (4-6 weeks) and long-term (6 months) active-controlled osteoarthritis trials:** abdominal pain, 2.3%, 2.9%; constipation, 1.2%, 2.6%; diarrhea, 2.7%, 2.6%; dyspepsia, 7.4%, 9.5%; flatulence, 0.4%, 2.6%; nausea, 4.7%, 7.2%; vomiting, 0.8%, 2.6%; edema[1], 2.0%, 1.6%; pain, 2.0%, 5.2%; dizziness, 1.6%, 2.6%; headache, 2.7%, 2.6%; anemia, 0.0%, 2.9%; arthralgia, 0.0%, 1.3%; back pain, 0.4%, 0.7%; insomnia, 0.0%, 1.6%; coughing, 0.8%, 1.0%; upper respiratory tract infection, 0.0%, 7.5%; pruritus, 1.2%, 0.0%; rash[2], 1.2%, 1.3%; micturition frequency, 0.4%, 1.3%; urinary tract infection, 0.4%, 6.9%.

[1]WHO preferred terms edema, edema dependent, edema peripheral and edema legs combined.

[2]WHO preferred terms rash, rash erythematous and rash maculo-papular combined.

**The following adverse events (%) occurred respectively with MOBIC 7.5 and 15 mg daily in ≥ 2% of patients treated in two 12-week rheumatoid arthritis placebo controlled trials:** abdominal pain NOS[2], 2.9%, 2.3%; diarrhea NOS[2], 4.8%, 3.4%; dyspeptic signs and symptoms[1], 5.8%, 4.0%; nausea[2], 3.3%, 3.8%; influenza like illness[2], 2.9% 2.3%; upper respiratory tract infections-pathogen class unspecified[1], 7.0%, 6.5%; joint related signs and symptoms[1], 1.5%, 2.3%; musculoskeletal and connective tissue signs and symptoms NEC[1], 1.7% 2.9%; headaches NOS[2], 6.4%, 5.5%; dizziness (excl vertigo)[2], 2.3%, 0.4%; rash NOS[2], 1.0%, 2.1%.

[1]MedDRA high level term (preferred terms): dyspeptic signs and symptoms (dyspepsia, dyspepsia aggravated, eructation, gastrointestinal irritation), upper respiratory tract infections-pathogen unspecified (laryngitis NOS, pharyngitis NOS, sinusitis NOS), joint related signs and symptoms (arthralgia, arthralgia aggravated, joint crepitation, joint effusion, joint swelling), and musculoskeletal and connective tissue signs and symptoms NEC (back pain, back pain aggravated, muscle spasms, musculoskeletal pain).

[2]MedDRA preferred term: diarrhea NOS, abdominal pain NOS, influenza like illness, headaches NOS, dizziness (excl vertigo), and rash NOS.

Higher doses of MOBIC (22.5 mg and greater) have been associated with an increased risk of serious GI events; therefore the daily dose of MOBIC should not exceed 15 mg.

**Pediatrics**

***Pauciarticular and Polyarticular Course Juvenile Rheumatoid Arthritis (JRA)***

Three hundred and eighty-seven patients with pauciarticular and polyarticular course JRA were exposed to MOBIC with doses ranging from 0.125 to 0.375 mg/kg per day in three clinical trials. These studies consisted of two 12-week multicenter, double-blind, randomized trials (one with a 12-week open-label extension and one with a 40-week extension) and one 1-year open-label PK study. The adverse events observed in these pediatric studies with MOBIC were similar in nature to the adult clinical trial experience, although there were differences in frequency. In particular, the following most common adverse events — abdominal pain, vomiting, diarrhea, headache, and pyrexia — were more common in the pediatric than in the adult trials. Rash was reported in seven (<2%) patients receiving MOBIC. No unexpected adverse events were identified during the course of the trials. The adverse events did not demonstrate an age or gender-specific subgroup effect.

The following is a list of adverse drug reactions occurring in < 2% of patients receiving MOBIC in clinical trials involving approximately 16,200 patients. Adverse reactions reported only in worldwide post-marketing experience or the literature are shown in italics and are considered rare (< 0.1%).

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| **Body as a Whole** | allergic reaction, *anaphylactoid reactions including shock*, face edema, fatigue, fever, hot flushes, malaise, syncope, weight decrease, weight increase |
| **Cardiovascular** | angina pectoris, cardiac failure, hypertension, hypotension, myocardial infarction, vasculitis |
| **Central and Peripheral Nervous System** | convulsions, paresthesia, tremor, vertigo |
| **Gastrointestinal** | colitis, dry mouth, duodenal ulcer, eructation, esophagitis, gastric ulcer, gastritis, gastroesophageal reflux, gastrointestinal hemorrhage, hematemesis, hemorrhagic duodenal ulcer, hemorrhagic gastric ulcer, intestinal perforation, melena, pancreatitis, perforated duodenal ulcer, perforated gastric ulcer, stomatitis ulcerative |
| **Heart Rate and Rhythm** | arrhythmia, palpitation, tachycardia |
| **Hematologic** | *agranulocytosis*, leukopenia, purpura, thrombocytopenia |
| **Liver and Biliary System** | ALT increased, AST increased, bilirubinemia, GGT increased, hepatitis, *jaundice, liver failure* |
| **Metabolic and Nutritional** | dehydration |
| **Psychiatric Disorders** | abnormal dreaming, anxiety, appetite increased, confusion, depression, nervousness, somnolence |