

# Methotrexate Prevents Further Arthritis Damage

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SAN DIEGO — For the first time, a randomized trial has demonstrated that treatment of early undifferentiated arthritis with methotrexate can prevent progression to rheumatoid arthritis. Dr. Henrike van Dongen reported in a late-breaking poster session at the annual meeting of the American College of Rheumatology. Findings from previous studies have

suggested that early treatment of rheumatoid arthritis (RA) can lessen severity or induce remission, but until now there have been no data to show that the same benefits can occur in patients with undifferentiated, or “probable,” arthritis.

In the Early Treatment of Probable Rheumatoid Arthritis Patients with Methotrexate (PROBAAT) trial, 110 patients who did not yet fulfill ACR criteria for RA were randomized to 15 mg/week of methotrexate or placebo.

## Status at 18 Months After Initial Diagnosis

	RA	UA	UA in Remission	OA	Lost to Follow-up
Methotrexate (n = 55)	20	13	18	1	3
Placebo (n = 55)	29	8	11	4	3

Source: Dr. van Dongen

The methotrexate dose was adjusted over time based on disease severity. At 3 months, the mean decrease in Dis-

ease Activity Severity (DAS) score was 0.39 in the methotrexate and 0.005 in the placebo group, a difference that was statistically significant.

At 18 months, fewer patients in the methotrexate group had developed RA and more had achieved remission, compared with those in the placebo group (see chart). Radiographic progression was significantly higher in the placebo group, noted Dr. van Dongen of Leiden (the Netherlands) University Medical Center.

## Extra Vitamin D Fails to Cut Pain Of Fibromyalgia

SAN DIEGO — Vitamin D supplementation did not lessen fibromyalgia symptoms in a small trial, a finding that casts doubt on the theory that vitamin D deficiency underlies some patients' pain and that screening vitamin D levels would identify patients who would benefit from supplementation, Dr. Ann Warner said in a poster presentation at the annual meeting of the American College of Rheumatology.

She performed two studies examining the vitamin D hypothesis. In one study, Dr. Warner, a rheumatologist who practices in Kansas City, Mo., took 50 fibromyalgia patients with insufficient serum levels of vitamin D (a 25-hydroxyvitamin D level less than 20 ng/mL) and randomized them to weekly doses of 50,000 IU of vitamin D or to placebo for 3 months.

The 25 patients randomized to supplementation had a higher mean pain score on a visual analog scale at baseline compared with the patients who received placebo (74 mm vs. 61 mm). The mean pain score of patients given supplemental vitamin D improved after 3 months, falling to 64 mm. However, the mean visual analog scale score of the control patients fell to a similar degree, to 54 mm, and neither group's changes were statistically significant.

Patients in the control group showed a slight, but significant improvement on the functional pain score, while the supplemented group did not.

In the second study, Dr. Warner compared 25-hydroxyvitamin D levels in 104 patients with osteoarthritis with levels in 184 fibromyalgia patients.

There was no statistically significant difference in mean levels between the groups (28.76 ng/mL for the osteoarthritis group vs. 29.16 for the fibromyalgia group) even though there was a slightly higher percentage of patients with fibromyalgia who were insufficient, 29% vs. 20%.

—Timothy F. Kirn

BENICAR® Tablets (olmesartan medoxomil)/BENICAR HCT® Tablets (olmesartan medoxomil-hydrochlorothiazide)

Although any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease), chloride replacement may be required in the treatment of metabolic alkalosis.

Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction, rather than administration of salt except in rare instances when the hyponatremia is life-threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Hyperuricemia may occur or frank gout may be precipitated in certain patients receiving thiazide therapy.

In diabetic patients dosage adjustments of insulin or oral hypoglycemic agents may be required. Hyperglycemia may occur with thiazide diuretics. Thus latent diabetes mellitus may become manifest during thiazide therapy.

The antihypertensive effects of the drug may be enhanced in the post-sympathectomy patient.

If progressive renal impairment becomes evident consider withholding or discontinuing diuretic therapy.

Thiazides have been shown to increase the urinary excretion of magnesium; this may result in hypomagnesemia.

Thiazides may decrease urinary calcium excretion. Thiazides may cause intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcemia may be evidence of hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.

Increases in cholesterol and triglyceride levels may be associated with thiazide diuretic therapy.

**Impaired Renal Function**  
As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals treated with olmesartan medoxomil. In patients whose renal function may depend upon the activity of the renin-angiotensin-aldosterone system (e.g., patients with severe congestive heart failure), treatment with angiotensin converting enzyme inhibitors and angiotensin receptor antagonists has been associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and/or death. Similar results may be anticipated in patients treated with olmesartan medoxomil. (See **CLINICAL PHARMACOLOGY, Special Populations** in the full prescribing information.)

In studies of ACE inhibitors in patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine or blood urea nitrogen (BUN) have been reported. There has been no long-term use of olmesartan medoxomil in patients with unilateral or bilateral renal artery stenosis, but similar results may be expected.

Thiazides should be used with caution in severe renal disease. In patients with renal disease, thiazides may precipitate azotemia. Cumulative effects of the drug may develop in patients with impaired renal function.

**Information for Patients**  
**Pregnancy:** Female patients of childbearing age should be told about the consequences of second and third trimester exposure to drugs that act on the renin-angiotensin system and they should be told also that these consequences do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible.

**Symptomatic Hypotension:** A patient receiving BENICAR HCT® should be cautioned that light-headedness can occur, especially during the first days of therapy, and that it should be reported to the prescribing physician. The patient should be told that if syncope occurs, BENICAR HCT® should be discontinued until the physician has been consulted.

All patients should be cautioned that inadequate fluid intake, excessive perspiration, diarrhea or vomiting can lead to an excessive fall in blood pressure, with the same consequences of light-headedness and possible syncope.

**Drug Interactions**  
**Olmesartan medoxomil**  
No significant drug interactions were reported in studies in which olmesartan medoxomil was co-administered with hydrochlorothiazide, digoxin or warfarin in healthy volunteers. The bioavailability of olmesartan was not significantly altered by the co-administration of antacids [Al(OH)<sub>3</sub>/Mg(OH)<sub>2</sub>]. Olmesartan medoxomil is not metabolized by the cytochrome P450 system and has no effects on P450 enzymes; thus, interactions with drugs that inhibit, induce or are metabolized by those enzymes are not expected.

**Hydrochlorothiazide**  
When administered concurrently the following drugs may interact with thiazide diuretics:

**Alcohol, Barbiturates, Or Narcotics** – potentiation of orthostatic hypotension may occur.

**Antidiabetic Drugs (oral agents and insulin)** – dosage adjustment of the antidiabetic drug may be required.

**Other Antihypertensive Drugs** – additive effect or potentiation.

**Cholestyramine and Colestipol Resins** – absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins. Single doses of either cholestyramine or colestipol bind the hydrochlorothiazide and reduce its absorption from the gastrointestinal tract by up to 85 and 43 percent, respectively.

**Corticosteroids, ACTH** – intensified electrolyte depletion, particularly hypokalemia.

**Pressor Amines (e.g., Norepinephrine)** – possible decreased response to pressor amines but not sufficient to preclude their use.

**Skeletal Muscle Relaxants, Non-depolarizing (e.g., Tubocurarine)** – possible increased responsiveness to the muscle relaxant.

**Lithium** – should not generally be given with diuretics. Diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity. Refer to the package insert for lithium preparations before use of such preparation with olmesartan medoxomil-hydrochlorothiazide.

**Non-steroidal Anti-inflammatory Drugs** – in some patients the administration of a non-steroidal anti-inflammatory agent can reduce the diuretic, natriuretic and anti-hypertensive effects of loop, potassium-sparing and thiazide diuretics. Therefore, when olmesartan medoxomil-hydrochlorothiazide tablets and non-steroidal anti-inflammatory agents are used concomitantly, the patients should be observed closely to determine if the desired effect of the diuretic is obtained.

**Carcinogenesis, Mutagenesis, Impairment of Fertility**

**Olmesartan medoxomil-hydrochlorothiazide**  
No carcinogenicity studies with olmesartan medoxomil-hydrochlorothiazide have been conducted.

Olmesartan medoxomil-hydrochlorothiazide in a ratio of 20:12.5 was negative in the *Salmonella-Escherichia coli*/mammalian microsome reverse mutation test up to the maximum recommended plate concentration for the standard assays.

Olmesartan medoxomil and hydrochlorothiazide were tested individually and in combination ratios of 40:12.5, 20:12.5 and 10:12.5, for clastogenic activity in the *in vitro* Chinese hamster lung (CHL) chromosomal aberration assay. A positive response was seen for each component and combination ratio. However, no synergism in clastogenic activity was detected between olmesartan medoxomil and hydrochlorothiazide at any combination ratio. Olmesartan medoxomil-hydrochlorothiazide in a ratio of 20:12.5, administered orally, tested negative in the *in vivo* mouse bone marrow erythrocyte micronucleus assay at administered doses of up to 3144 mg/kg.

No studies of impairment of fertility with olmesartan medoxomil-hydrochlorothiazide have been conducted.

**Olmesartan medoxomil**  
Olmesartan medoxomil was not carcinogenic when administered by dietary administration to rats for up to 2 years. The highest dose tested (2000 mg/kg/day) was, on a mg/m<sup>2</sup> basis, about 400 times the maximum recommended human dose (MRHD) of 40 mg/day. Two carcinogenicity studies conducted in mice, a 6-month gavage study in the p53 knockout mouse and a 6-month dietary

administration study in the Hras2 transgenic mouse, at doses of up to 1000 mg/kg/day (about 120 times the MRHD), revealed no evidence of a carcinogenic effect of olmesartan medoxomil.

Both olmesartan medoxomil and olmesartan tested negative in the *in vitro* Syrian hamster embryo cell transformation assay and showed no evidence of genetic toxicity in the Ames (bacterial mutagenicity) test. However, both were shown to induce chromosomal aberrations in cultured cells *in vitro* (Chinese hamster lung) and both tested positive for thymidine kinase mutations in the *in vitro* mouse lymphoma assay. Olmesartan medoxomil tested negative *in vivo* for mutations in the Mutamouse intestine and kidney, and for clastogenicity in mouse bone marrow (micronucleus test) at oral doses of up to 2000 mg/kg (olmesartan not tested).

Fertility of rats was unaffected by administration of olmesartan medoxomil at dose levels as high as 1000 mg/kg/day (240 times the MRHD) in a study in which dosing was begun 2 (female) or 9 (male) weeks prior to mating.

**Hydrochlorothiazide**  
Two-year feeding studies in mice and rats conducted under the auspices of the National Toxicology Program (NTP) uncovered no evidence of a carcinogenic potential of hydrochlorothiazide in female mice (at doses of up to approximately 600 mg/kg/day) or in male and female rats (at doses of up to approximately 100 mg/kg/day). The NTP, however, found equivocal evidence for hepatocarcinogenicity in male mice.

Hydrochlorothiazide was not genotoxic *in vivo* in the Ames mutagenicity assay of *Salmonella typhimurium* strains TA 98, TA 100, TA 1538, TA 1537 and TA 1538, or in the Chinese Hamster Ovary (CHO) test for chromosomal aberrations. It was also not genotoxic *in vitro* in assays using mouse germinal cell chromosomes, Chinese hamster bone marrow chromosomes, or the *Drosophila* sex-linked recessive lethal trait gene. Positive test results were obtained in the *in vitro* CHO Sister Chromatid Exchange (clastogenicity) assay, the Mouse Lymphoma Cell (mutagenicity) assay and the *Aspergillus nidulans* non-disjunction assay.

Hydrochlorothiazide had no adverse effects on the fertility of mice and rats of either sex in studies wherein these species were exposed, via their diet, to doses of up to 100 and 4 mg/kg, respectively, prior to mating and throughout gestation.

**Pregnancy**  
Pregnancy Categories C (first trimester) and D (second and third trimesters) (See **WARNINGS: Fetal/Neonatal Morbidity and Mortality**.)

**Nursing Mothers**  
It is not known whether olmesartan is excreted in human milk, but olmesartan is secreted at low concentration in the milk of lactating rats. Because of the potential for adverse effects on the nursing infant, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Thiazides appear in human milk. Because of the potential for adverse effects on the nursing infant, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

**Pediatric Use**  
Safety and effectiveness in pediatric patients have not been established.

**Geriatric Use**  
Clinical studies of BENICAR HCT® did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function and of concomitant diseases or other drug therapy.

Olmesartan and hydrochlorothiazide are substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function.

**ADVERSE REACTIONS**  
**Olmesartan medoxomil-hydrochlorothiazide**  
Olmesartan medoxomil-hydrochlorothiazide has been evaluated for safety in 1243 hypertensive patients. Treatment with olmesartan medoxomil-hydrochlorothiazide was well tolerated, with an incidence of adverse events similar to placebo. Events generally were mild, transient and had no relationship to the dose of olmesartan medoxomil-hydrochlorothiazide.

In the clinical trials, the overall frequency of adverse events was not dose-related. Analysis of gender, age and race groups demonstrated no differences between olmesartan medoxomil-hydrochlorothiazide and placebo-treated patients. The rate of withdrawals due to adverse events in all trials of hypertensive patients was 2.0% (25/1243) of patients treated with olmesartan medoxomil-hydrochlorothiazide and 2.0% (7/342) of patients treated with placebo.

In a placebo-controlled clinical trial, the following adverse events reported with olmesartan medoxomil-hydrochlorothiazide occurred in >2% of patients, and more often on the olmesartan medoxomil-hydrochlorothiazide combination than on placebo, regardless of drug relationship:

	Olmesartan/ HCT (N=247) (%)	Placebo (N=42) (%)	Olmesartan (N=125) (%)	HCT (N=88) (%)
<b>Gastrointestinal</b>				
Nausea	3	0	2	1
<b>Metabolic</b>				
Hyperuricemia	4	2	0	2
<b>Nervous System</b>				
Dizziness	9	2	1	8
<b>Respiratory</b>				
Upper Respiratory Tract Infection	7	0	6	7

The following adverse events were also reported at a rate of >2%, but were as, or more, common in the placebo group: headache and urinary tract infection. Other adverse events that have been reported with an incidence of greater than 1.0%, whether or not attributed to treatment, in the more than 1200 hypertensive patients treated with olmesartan medoxomil-hydrochlorothiazide in controlled or open-label trials are listed below.

**Body as a Whole:** chest pain, back pain, peripheral edema  
**Central and Peripheral Nervous System:** vertigo  
**Gastrointestinal:** abdominal pain, dyspepsia, gastroenteritis, diarrhea  
**Liver and Biliary System:** SGOT increased, GGT increased, SGPT increased  
**Metabolic and Nutritional:** hyperlipidemia, hyperuricemia, hyperphosphatemia increased, hyperglycemia  
**Musculoskeletal:** arthritis, arthralgia, myalgia  
**Respiratory System:** coughing  
**Skin and Appendages Disorders:** rash  
**Urinary System:** hematuria

Facial edema was reported in 2/1243 patients receiving olmesartan medoxomil-hydrochlorothiazide. Angioedema has been reported with angiotensin II receptor antagonists.

**Olmesartan medoxomil**  
Other adverse events that have been reported with an incidence of greater than 0.5%, whether or not attributed to treatment, in more than 3100 hypertensive patients treated with olmesartan medoxomil monotherapy in controlled or open-label trials are tachycardia and hypercholesterolemia.

**Hydrochlorothiazide**  
Other adverse experiences that have been reported with hydrochlorothiazide, without regard to causality, are listed below:

**Body as a Whole:** weakness  
**Digestive:** pancreatitis, jaundice (intrahepatic cholestatic jaundice), sialadenitis, cramping, gastric irritation  
**Hematologic:** aplastic anemia, agranulocytosis, leukopenia, hemolytic anemia, thrombocytopenia  
**Hypersensitivity:** purpura, photosensitivity, urticaria, necrotizing angitis (vasculitis and cutaneous vasculitis), fever, respiratory distress including pneumonitis and pulmonary edema, anaphylactic reactions  
**Metabolic:** hyperglycemia, glycosuria, hyperuricemia  
**Musculoskeletal:** muscle spasm  
**Nervous System/Psychiatric:** restlessness  
**Renal:** renal failure, renal dysfunction, interstitial nephritis  
**Skin:** erythema multiforme including Stevens-Johnson syndrome, exfoliative dermatitis including toxic epidermal necrolysis  
**Special Senses:** transient blurred vision, xanthopsia

**Laboratory Test Findings**  
In controlled clinical trials, clinically important changes in standard laboratory parameters were rarely associated with administration of olmesartan medoxomil-hydrochlorothiazide.

**Creatinine, Blood Urea Nitrogen:** Increases in blood urea nitrogen (BUN) and serum creatinine of >50% were observed in 1.3% of patients. No patients were discontinued from clinical trials of olmesartan medoxomil-hydrochlorothiazide due to increased BUN or creatinine.

**Hemoglobin and Hematocrit:** A greater than 20% decrease in hemoglobin and hematocrit was observed in 0.0% and 0.4% (one patient), respectively, of olmesartan medoxomil-hydrochlorothiazide patients, compared with 0.0% and 0.0%, respectively, in placebo-treated patients. No patients were discontinued due to anemia.

**Post-Marketing Experience:** The following adverse reactions have been reported in post-marketing experience:

**Body as a Whole:** Asthenia, angioedema  
**Gastrointestinal:** Vomiting  
**Musculoskeletal:** Rhabdomyolysis  
**Urogenital System:** Acute renal failure, increased blood creatinine levels  
**Skin and Appendages:** Alopecia, pruritus, urticaria

**OVERDOSAGE**  
**Olmesartan medoxomil**  
Limited data are available related to overdosage in humans. The most likely manifestations of overdosage would be hypotension and tachycardia; bradycardia could be encountered if parasympathetic (vagal) stimulation occurs. If symptomatic hypotension should occur, supportive treatment should be initiated. The dialyzability of olmesartan is unknown.

No lethality was observed in acute toxicity studies in mice and rats given single oral doses up to 2000 mg/kg olmesartan medoxomil. The minimum lethal oral dose of olmesartan medoxomil in dogs was greater than 1500 mg/kg.

**Hydrochlorothiazide**  
The most common signs and symptoms of overdose observed in humans are those caused by electrolyte depletion (hypokalemia, hypochloremia, hyponatremia) and dehydration resulting from excessive diuresis. If digitalis has also been administered, hypokalemia may accentuate cardiac arrhythmias. The degree to which hydrochlorothiazide is removed by hemodialysis has not been established. The oral LD<sub>50</sub> of hydrochlorothiazide is greater than 10 g/kg in both mice and rats.

**DOSAGE AND ADMINISTRATION**  
The usual recommended starting dose of BENICAR® (olmesartan medoxomil) is 20 mg once daily when used as monotherapy in patients who are not volume-contracted. For patients requiring further reduction in blood pressure after 2 weeks of therapy, the dose may be increased to 40 mg. Doses above 40 mg do not appear to have greater effect. Twice-daily dosing offers no advantage over the same total dose given once daily.

No initial dosage adjustment is recommended for elderly patients, for patients with moderate to marked renal impairment (creatinine clearance <40 mL/min) or with moderate to marked hepatic dysfunction (see **CLINICAL PHARMACOLOGY, Special Populations** in the full prescribing information). For patients with possible depletion of intravascular volume (e.g., patients treated with diuretics, particularly those with impaired renal function), BENICAR® should be initiated under close medical supervision and consideration should be given to use of a lower starting dose (see **WARNINGS, Hypotension in Volume- or Salt-Depleted Patients**).

Hydrochlorothiazide is effective in doses between 12.5 mg and 50 mg once daily. The side effects (see **WARNINGS**) of BENICAR® are generally rare and independent of dose; those of hydrochlorothiazide are most typically dose-dependent (primarily hypokalemia). Some dose-independent phenomena (e.g., pancreatitis) do occur with hydrochlorothiazide. Therapy with any combination of olmesartan medoxomil and hydrochlorothiazide will be associated with both sets of dose-independent side effects.

To minimize dose-independent side effects, it is usually appropriate to begin combination therapy only after a patient has failed to achieve the desired effect with monotherapy.

**Replacement Therapy**  
BENICAR HCT® (olmesartan medoxomil-hydrochlorothiazide) may be substituted for its titrated components.

**Dose Titration by Clinical Effect**  
BENICAR HCT® is available in strengths of 20 mg/12.5 mg, 40 mg/12.5 mg and 40 mg/25 mg. A patient whose blood pressure is inadequately controlled by BENICAR® or hydrochlorothiazide alone may be switched to once daily BENICAR HCT® (olmesartan medoxomil-hydrochlorothiazide).

Dosing should be individualized. Depending on the blood pressure response, the dose may be titrated at intervals of 2-4 weeks.

If blood pressure is not controlled by BENICAR® alone, hydrochlorothiazide may be added starting with a dose of 12.5 mg and later titrated to 25 mg once daily. If a patient is taking hydrochlorothiazide, BENICAR® may be added starting with a dose of 20 mg once daily and titrated to 40 mg, for inadequate blood pressure control. If large doses of hydrochlorothiazide have been used as monotherapy and volume depletion or hyponatremia is present, caution should be used when adding BENICAR® or switching to BENICAR HCT® as marked decreases in blood pressure may occur (see **WARNINGS, Hypotension in Volume- or Salt-Depleted Patients**). Consideration should be given to reducing the dose of hydrochlorothiazide to 12.5 mg before adding BENICAR®.

The antihypertensive effect of BENICAR HCT® is related to the dose of both components over the range of 10 mg/12.5 mg to 40 mg/25 mg (see **CLINICAL PHARMACOLOGY, Clinical Trials** in the full prescribing information). The dose of BENICAR HCT® is one tablet once daily. More than one tablet daily is not recommended.

BENICAR HCT® may be administered with other antihypertensive agents.

**Patients with Renal Impairment**  
The usual regimens of therapy with BENICAR HCT® may be followed provided the patient's creatinine clearance is >30 mL/min. In patients with more severe renal impairment, loop diuretics are preferred to thiazides, so BENICAR HCT® is not recommended.

**Patients with Hepatic Impairment**  
No dosage adjustment is necessary with hepatic impairment (see **CLINICAL PHARMACOLOGY, Special Populations** in the full prescribing information).

Manufactured for Sankeyo Pharma Inc., Parsippany, NJ 07054

**Rx Only**

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