# All DMARD Patients Need Hepatitis Screening

BY BRUCE JANCIN

SNOWMASS, COLO. — Screening for both hepatitis C and B is a reasonable strategy in all patients who are under consideration for any disease-modifying antirheumatic drug. "If they turn out to be infected, you've done them a huge favor. Send them to a hepatologist for treatment," advised Dr. Leonard H. Calabrese.

And just because they have chronic viral hepatitis doesn't mean that their comorbid rheumatic disease can't be aggressively treated, provided they don't have decompensated liver disease and are Child-Pugh class A, he stressed at a symposium sponsored by the American College of Rheumatology.

In fact, there is evidence to suggest that in the setting of chronic HCV, anti–tumor necrosis factor (anti-TNF) therapy is not only safe, it actually may also substantially improve the tolerability of antiviral therapy with interferon and ribavirin, thereby boosting the hepatitis cure rate, according to Dr. Calabrese.

This possibility was first broached a half-decade ago in a positive double-blind, placebo-controlled, phase II study of etanercept (Enbrel) (J. Hepatol. 2005;42:315-22). The manufacturer resisted hepatologists' subsequent pleas to mount a definitive clinical trial. However, such a study is now underway using another anti-TNF drug, infliximab (Remicade).

The 52-week, multicenter, blinded, randomized PARTNER (Pegylated Interferon Ribavirin and Anti-TNF Enhanced Response) trial, sponsored by the Cleveland Clinic, has completed just over half of its enrollment. Eligibility is


MICARDIS® (telmisartan) tablets 20•40•80 mg

**WARNING: AVOID USE IN PREGNANCY**
**When used in pregnancy, drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus.** When pregnancy is detected, MICARDIS tablets should be discontinued as soon as possible. *See Warnings and Precautions*.

**BRIEF SUMMARY OF PRESCRIBING INFORMATION**

**INDICATIONS AND USAGE**

**Hypertension**

MICARDIS is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents.

**Cardiovascular Risk Reduction**

MICARDIS is indicated for reduction of the risk of myocardial infarction, stroke, or death from cardiovascular causes in patients 55 years of age or older at high risk of developing major cardiovascular events who are unable to take ACE inhibitors.

High risk for cardiovascular events can be evidenced by a history of coronary artery disease, peripheral arterial disease, stroke, transient ischemic attack, or high-risk diabetes (insulin-dependent or non-insulin dependent) with evidence of end-organ damage. MICARDIS can be used in addition to other needed treatment (such as antihypertensive, antiplatelet or lipid-lowering therapy).

Studies of telmisartan in this setting do not exclude that it may not preserve a meaningful fraction of the effect of the ACE inhibitor to which it was compared. Consider using the ACE inhibitor first, and, if it is stopped for cough only, consider re-trying the ACE inhibitor after the cough resolves.

Use of telmisartan with an ACE inhibitor is not recommended.

**CONTRAINDICATIONS**

None.

**WARNINGS AND PRECAUTIONS**

**Fetal/Neonatal Morbidity and Mortality**

Drugs that act directly on the renin-angiotensin system can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature in patients who were taking angiotensin converting enzyme inhibitors. When pregnancy is detected, discontinue MICARDIS tablets as soon as possible [*see Boxed Warning*].

The use of drugs that act directly on the renin-angiotensin system during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to exposure to the drug.

These adverse effects do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester. Inform mothers whose embryos and fetuses are exposed to an angiotensin II receptor antagonist only during the first trimester that most reports of fetal toxicity have been associated with second and third trimester exposure. Nonetheless, when patients become pregnant or are considering pregnancy, have the patient discontinue the use of MICARDIS tablets as soon as possible.

Rarely (probably less often than once in every thousand pregnancies), no alternative to an angiotensin II receptor antagonist will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intra-amniotic environment.

If oligohydramnios is observed, MICARDIS should be discontinued unless they are considered life-saving for the mother. Contraction stress testing (CST), a non-stress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Infants with histories of *in utero* exposure to an angiotensin II receptor antagonist should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as a means of reversing hypotension and/or substituting for disordered renal function.

**Hypotension**

In patients with an activated renin-angiotensin system, such as volume- and/or salt-depleted patients (e.g., those being treated with high doses of diuretics), symptomatic hypotension may occur after initiation of therapy with MICARDIS. Either correct this condition prior to administration of MICARDIS, or start treatment under close medical supervision with a reduced dose.

If hypotension does occur, the patient should be placed in the supine position and, if necessary, given an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further treatment, which usually can be continued without difficulty once the blood pressure has stabilized.

**Hyperkalemia**

Hyperkalemia may occur in patients on ARBs, particularly in patients with advanced renal impairment, heart failure, on renal replacement therapy, or on potassium supplements, potassium-sparing diuretics, potassium-containing salt substitutes or other drugs that increase potassium levels. Consider periodic determinations of serum electrolytes to detect possible electrolyte imbalances, particularly in patients at risk.

**Impaired Hepatic Function**

As the majority of telmisartan is eliminated by biliary excretion, patients with biliary obstructive disorders or hepatic insufficiency can be expected to have reduced clearance. Initiate telmisartan at low doses and titrate slowly in these patients.

**Impaired Renal Function**

As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients whose renal function may depend on the activity of the renin-angiotensin-aldosterone system (e.g., patients with severe congestive heart failure or renal dysfunction), treatment with angiotensin-converting enzyme (ACE) 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 have been reported with MICARDIS.

In studies of ACE inhibitors in patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine or blood urea nitrogen were observed. There has been no long term use of MICARDIS in patients with unilateral or bilateral renal artery stenosis but anticipate an effect similar to that seen with ACE inhibitors.

**Dual Blockade of the Renin-Angiotensin-Aldosterone System**

As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function (including acute renal failure) have been reported. Dual blockade of the renin-angiotensin-aldosterone system (e.g., by adding an ACE-inhibitor to an angiotensin II receptor antagonist) should include close monitoring of renal function.

The ONTARGET trial enrolled 25,620 patients ≥55 years old with atherosclerotic disease or diabetes with end-organ damage, randomizing them to telmisartan only, ramipril only, or the combination, and followed them for a median of 56 months. Patients receiving the combination of MICARDIS and ramipril did not obtain any additional benefit compared to monotherapy, but experienced an increased incidence of renal dysfunction (e.g., acute renal failure) compared with groups receiving telmisartan alone or ramipril alone. Concomitant use of MICARDIS and ramipril is not recommended.

**ADVERSE REACTIONS**

The following adverse reaction is described elsewhere in labeling:

Renal dysfunction upon use with ramipril.

**Clinical Trials Experience**

Because clinical studies are conducted under widely varying conditions, adverse reactions rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

*Hypertension*

MICARDIS has been evaluated for safety in more than 3700 patients, including 1900 treated for over six months and more than 1300 for over one year. Adverse experiences have generally been mild and transient in nature and have infrequently required discontinuation of therapy.

In placebo-controlled trials involving 1041 patients treated with various doses of MICARDIS (20-160 mg) monotherapy for up to 12 weeks, the overall incidence of adverse events was similar to that in patients treated with placebo.

Adverse events occurring at an incidence of ≥1% in patients treated with MICARDIS and at a greater rate than in patients treated with placebo, irrespective of their causal association, are presented in Table 1.

**Table 1 Adverse Events Occurring at an Incidence of ≥ 1% in Patients Treated with MICARDIS and at a Greater Rate Than in Patients Treated with Placebo**

| | Telmisartan (n=1455) % | Placebo (n=380) % |
|---|---|---|
| Upper respiratory tract infection | 7 | 6 |
| Back pain | 3 | 1 |
| Sinusitis | 3 | 2 |
| Diarrhea | 3 | 2 |
| Pharyngitis | 1 | 0 |

restricted to patients with chronic HCV with genotype 1, the most treatment-resistant form of the liver disease. As in the etanercept study, these hepatitis C patients don't have concomitant rheumatic disease; they are being randomized to anti-TNF therapy solely in an effort to improve the results of their antiviral regimen.

However, several reports published in the rheumatology literature point to the safety of anti-TNF therapy in patients with chronic HCV and comorbid rheumatic diseases. Dr. Calabrese highlighted what he termed a "thoughtful and reassuring" seven-center prospective Italian series involving 31 chronic HCV-infected patients with rheumatoid arthritis (RA) refractory to nonbiologic disease-modifying antirheumatic drugs (DMARDs). After a mean 22 months of treatment with infliximab, etanercept, or adalimumab, the patients showed marked lessening of their rheumatic disease with no adverse effects on liver enzymes or HCV viral load (J. Rheumatol. 2008;35:1944-9).

Based largely on such favorable reports as well as the results of the earlier etanercept study, Dr. Calabrese reported that he turns to anti-TNF biologic agents as first-line therapy in HCV-infected patients who require remittive therapy for a rheumatic disease. He makes sure they have a baseline liver biopsy, carefully monitors their liver enzymes, and considers rebiopsy at 3-5 years.

"At this point in time, there are more data on the safety of biologics than nonbiologic DMARDs in the setting of HCV," said Dr. Calabrese, who is professor of medicine at the Cleveland Clinic Foundation.

The use of DMARDs in patients with chronic HBV is a considerably more complex issue. That's because there is evidence that any form of immunosuppressive therapy—biologics, older DMARDs, or moderate- or high-dose systemic corticosteroids—can trigger a severe or even fatal flare of hepatitis B if the therapy is interrupted or discontinued.

Nonetheless, there are multiple reports of HBV-infected patients who are being successfully treated for rheumatoid arthritis and other rheumatic diseases with biologic agents or conventional DMARDs, provided they are started on prophylactic antiviral therapy beforehand. For example, Italian investigators reported no cases of HBV reactivation in 20 patients with rheumatic diseases who were treated with biologic DMARDs during a median 19 months of prophylactic antiviral therapy with lamivudine at 100 mg/day (Reumatismo. 2008;60:22-7).

**'There are more data on the safety of biologics than nonbiologic DMARDs in the setting of HCV.'**

DR. CALABRESE

Today, there are much better antivirals than lamivudine for this purpose, Dr. Calabrese pointed out. Nucleotide analog reverse transcriptase inhibitors such as adefovir (Preveon) and tenofovir (Viread) are very easy to use and have far fewer resistance issues. The experience to date strongly suggests that the newer agents can be given for the patient's full remaining life span.

There are at present no consensus guidelines in rheumatology that address screening for HCV and HBV. Dr. Calabrese advocated screening liberally; these are two of the biggest public health problems of the era, and treatment has progressed rapidly. He believes that all candidates for DMARD therapy ought to be screened, because at present there aren't enough data to say for sure that any of these agents are safe in the setting of viral hepatitis.

He also encouraged the screening of any rheumatology patient who is at high risk for HCV or HBV. For HBV, that would include anyone who's sexually active. For HCV, the high-risk population includes injectors of illegal drugs, individuals who engage in high-risk sexual activity, and anyone who received a blood transfusion before 1992.

Screening for HCV simply entails ordering a serum HCV antibody test. To screen for HBV, Dr. Calabrese likes to get a hepatitis B surface antigen (HBsAg), antibody to hepatitis B surface antigen (anti-HBs), and antibody to hepatitis B core antigen (anti-HBc).

"HBsAg is what you're really looking for. If you're positive, you're a carrier and you're infected," he said. ■

***Disclosures:*** *Dr. Calabrese disclosed serving as a paid consultant to Genentech, Roche, Amgen, Centocor, UCB Pharma, Sanofi-Aventis, and Wyeth.*

In addition to the adverse events in the table, the following events occurred at a rate of ≥1% but were at least as frequent in the placebo group: influenza-like symptoms, dyspepsia, myalgia, urinary tract infection, abdominal pain, headache, dizziness, pain, fatigue, coughing, hypertension, chest pain, nausea, and peripheral edema. Discontinuation of therapy because of adverse events was required in 2.8% of 1455 patients treated with Micardis® (telmisartan) tablets and 6.1% of 380 placebo patients in placebo-controlled clinical trials.

The incidence of adverse events was not dose-related and did not correlate with gender, age, or race of patients.

The incidence of cough occurring with telmisartan in 6 placebo-controlled trials was identical to that noted for placebo-treated patients (1.6%).

In addition to those listed above, adverse events that occurred in more than 0.3% of 3500 patients treated with MICARDIS monotherapy in controlled or open trials are listed below. It cannot be determined whether these events were causally related to MICARDIS tablets:

*Autonomic Nervous System*: impotence, increased sweating, flushing; *Body as a Whole*: allergy, fever, leg pain, malaise; *Cardiovascular*: palpitation, dependent edema, angina pectoris, tachycardia, leg edema, abnormal ECG; *CNS*: insomnia, somnolence, migraine, vertigo, paresthesia, involuntary muscle contractions, hypoaesthesia; *Gastrointestinal*: flatulence, constipation, gastritis, vomiting, dry mouth, hemorrhoids, gastroenteritis, enteritis, gastroesophageal reflux, toothache, non-specific gastrointestinal disorders; *Metabolic*: gout, hypercholesterolemia, diabetes mellitus; *Musculoskeletal*: arthritis, arthralgia, leg cramps; *Psychiatric*: anxiety, depression, nervousness; *Resistance Mechanism*: infection, fungal infection, abscess, otitis media; *Respiratory*: asthma, bronchitis, rhinitis, dyspnea, epistaxis; *Skin*: dermatitis, rash, eczema, pruritus; *Urinary*: micturition frequency, cystitis; *Vascular*: cerebrovascular disorder; and *Special Senses*: abnormal vision, conjunctivitis, tinnitus, earache.

During initial clinical studies, a single case of angioedema was reported (among a total of 3781 patients treated).

*Clinical Laboratory Findings*

In placebo-controlled clinical trials, clinically relevant changes in standard laboratory test parameters were rarely associated with administration of MICARDIS tablets.

Hemoglobin: A greater than 2 g/dL decrease in hemoglobin was observed in 0.8% telmisartan patients compared with 0.3% placebo patients. No patients discontinued therapy due to anemia.

Creatinine: A 0.5 mg/dL rise or greater in creatinine was observed in 0.4% telmisartan patients compared with 0.3% placebo patients. One telmisartan-treated patient discontinued therapy due to increases in creatinine and blood urea nitrogen.

Liver Enzymes: Occasional elevations of liver chemistries occurred in patients treated with telmisartan; all marked elevations occurred at a higher frequency with placebo. No telmisartan-treated patients discontinued therapy due to abnormal hepatic function.

*Cardiovascular Risk Reduction*

Because common adverse reactions were well characterized in studies of telmisartan in hypertension, only adverse events leading to discontinuation and serious adverse events were recorded in subsequent studies of telmisartan for cardiovascular risk reduction. In TRANSCEND (N=5926, 4 years and 8 months of follow-up), discontinuations for adverse events were 8.4% on telmisartan and 7.6% on placebo. The only serious adverse events at least 1% more common on telmisartan than placebo were intermittent claudication (7% vs 6%) and skin ulcer (3% vs 2%).

**Postmarketing Experience**

The following adverse reactions have been identified during post-approval use of MICARDIS. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to estimate reliably their frequency or establish a causal relationship to drug exposure. Decisions to include these reactions in labeling are typically based on one or more of the following factors: (1) seriousness of the reaction, (2) frequency of reporting, or (3) strength of causal connection to MICARDIS.

The most frequently spontaneously reported events include: headache, dizziness, asthenia, coughing, nausea, fatigue, weakness, edema, face edema, lower limb edema, angioneurotic edema, urticaria, hypersensitivity, sweating increased, erythema, chest pain, atrial fibrillation, congestive heart failure, myocardial infarction, blood pressure increased, hypertension aggravated, hypotension (including postural hypotension), hyperkalemia, syncope, dyspepsia, diarrhea, pain, urinary tract infection, erectile dysfunction, back pain, abdominal pain, muscle cramps (including leg cramps), myalgia, bradycardia, eosinophilia, thrombocytopenia, uric acid increased, abnormal hepatic function/liver disorder, renal impairment including acute renal failure, anemia, increased CPK, anaphylactic reaction, and tendon pain (including tendonitis, tenosynovitis).

Rare cases of rhabdomyolysis have been reported in patients receiving angiotensin II receptor blockers, including MICARDIS.

**DRUG INTERACTIONS**

*Digoxin:* When MICARDIS was co-administered with digoxin, median increases in digoxin peak plasma concentration (49%) and in trough concentration (20%) were observed. Therefore, monitor digoxin levels when initiating, adjusting, and discontinuing telmisartan for the purpose of keeping the digoxin level within the therapeutic range.

*Lithium:* Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with angiotensin II receptor antagonists including MICARDIS. Therefore, monitor serum lithium levels during concomitant use.

*Ramipril and Ramiprilat:* Co-administration of telmisartan 80 mg once daily and ramipril 10 mg once daily to healthy subjects increases steady-state $C_{max}$ and AUC of ramipril 2.3- and 2.1-fold, respectively, and $C_{max}$ and AUC of ramiprilat 2.4- and 1.5-fold, respectively. In contrast, $C_{max}$ and AUC of telmisartan decrease by 31% and 16%, respectively. When co-administering telmisartan and ramipril, the response may be greater because of the possibly additive pharmacodynamic effects of the combined drugs, and also because of the increased exposure to ramipril and ramiprilat in the presence of telmisartan. Concomitant use of MICARDIS and ramipril is not recommended.

*Other Drugs:* Co-administration of telmisartan did not result in a clinically significant interaction with acetaminophen, amlodipine, glyburide, simvastatin, hydrochlorothiazide, warfarin, or ibuprofen. Telmisartan is not metabolized by the cytochrome P450 system and had no effects *in vitro* on cytochrome P450 enzymes, except for some inhibition of CYP2C19. Telmisartan is not expected to interact with drugs that inhibit cytochrome P450 enzymes; it is also not expected to interact with drugs metabolized by cytochrome P450 enzymes, except for possible inhibition of the metabolism of drugs metabolized by CYP2C19.

**USE IN SPECIFIC POPULATIONS**

**Pregnancy**

***Teratogenic Effects,*** *Pregnancy Categories C (first trimester) and D (second and third trimesters). See Warnings and Precautions*.

**Nursing Mothers**

It is not known whether telmisartan is excreted in human milk, but telmisartan was shown to be present in the milk of lactating rats. Because of the potential for adverse effects on the nursing infant, decide 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**

Of the total number of patients receiving MICARDIS in hypertension clinical studies, 551 (19%) were 65 to 74 years of age and 130 (4%) were 75 years or older. No overall differences in effectiveness and safety were observed in these patients compared to younger patients and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Of the total number of patients receiving MICARDIS in the cardiovascular risk reduction study (ONTARGET), the percentage of patients ≥65 to <75 years of age was 42%; 15% of patients were ≥75 years old. No overall differences in effectiveness and safety were observed in these patients compared to younger patients and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

**Hepatic Insufficiency**

Monitor carefully and uptitrate slowly in patients with biliary obstructive disorders or hepatic insufficiency.

**OVERDOSAGE**

Limited data are available with regard to overdosage in humans. The most likely manifestation of overdosage with MICARDIS tablets would be hypotension, dizziness and tachycardia; bradycardia could occur from parasympathetic (vagal) stimulation. If symptomatic hypotension should occur, supportive treatment should be instituted. Telmisartan is not removed by hemodialysis.

**Rx only**

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