Gene Protective in Asthma, Smoking, COPD

BY MARY ANN MOON

A variation in the MMP12 gene appears to be associated with beneficial pulmonary effects in children who have asthma and in adults who smoke, particularly smokers with chronic obstructive pulmonary disease, according to a study in more than 8,000 patients.

"Our results suggest that variants of MMP12 are determinants of the level of lung function in subjects who are at risk for airflow obstruction," said Dr. Gary M. Hunninghake of Brigham and Women's Hospital, Boston, and his associates.

The investigators tested for an association between single nucleotide polymorphisms (SNPs) in the MMP12 gene and lung function as assessed by forced expiratory volume in 1 second (FEV_1) in cohorts participating in seven clinical trials. The MMP12 gene encodes matrix metalloproteinase 12, which is produced by macrophages, "the predominant cell type that patrols the lower airspaces under normal conditions and the main inflammatory cell type that is recruited with smoking," the investigators noted.

The researchers first found that the minor allele of SNP rs2276109 in the MMP12 gene was significantly associated with increased FEV_1 in children with asthma (but not nonasthmatic children) who were subjects in the Genetics of Asthma in Costa Rica Study. They then found the same link between the SNP and increased FEV_1 among children taking budesonide—but not among those who were not taking budesonide—in the Childhood Asthma Management Program. The same link between the SNP and increased FEV_1 existed among children with asthma (but not nonasthmatic children) in the BAMSE (Children, Allergy, Milieu, Stockholm, Epidemiological Survey) study.

Dr. Hunninghake and his colleagues then tested for the same association in adults who were subjects in the Boston Early-Onset COPD Study, the Lovelace Smokers Cohort, and the Normative Aging Study. The researchers found that the same SNP variation was associated with improved lung function in adults who were current or former smokers, but not in nonsmokers.

Finally, the investigators found that the same MMP12 variant appeared to protect patients at risk for COPD against the disease in those same three adult cohorts. The absence of the SNP rs2276109 was associated with a 54% increase in the risk of the onset of COPD and a population attributable risk of COPD of 28%.

The findings support the so-called "Dutch hypothesis," which states that asthma and COPD are different manifestations of a single disease entity and suggests that as-yet unknown genetic variants may underlie both asthma and COPD, the authors said (N. Engl. J. Med. 2009; 361[doi:10.1056/NEJMoa0904006]).

Most previous studies of genetic associations in pulmonary function have relied on a single cohort, the authors noted. "A strength of our study is that it included the analysis of multiple measurements of pulmonary function in a large number of subjects—more than 20,000 FEV_1 measurements in more than 8,300 subjects."

"Evidence is accumulating that asthma and COPD share common pathogenetic pathways," noted Dr. Guy G. Brusselle of Ghent (Belgium) University Hospital, in an editorial. The study "adds to the accumulating evidence that several mechanisms may lead to the development of COPD" (N. Engl. J. Med. 2009;361 [doi:10.1056/NEJMe0919626]).

The new study has several strengths, Dr. Brusselle noted. Those strengths include the inclusion of seven cohorts with more than 8,300 subjects; the replication of an association between the SNP and FEV_1 both in adult smokers and children with asthma; and the researchers' ability to repeat the analyses after stratification for asthma status and smoking status. ■

Disclosures: Dr. Hunninghake reported no conflicts of interest relevant to the study. His associates reported receiving support from AstraZeneca Pharmaceuticals, Merck & Co., Johnson & Johnson, Golden Helix, Novartis, GlaxoSmithKline, Sandvik, Sepracor, Genentech, and Phadia AB.

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

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 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%). In clinical studies with patients at high risk of developing major cardiovascular events, cases of sepsis, including some with fatal outcomes, have been reported. **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.

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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