Trial Quantifies Exercise Benefits in Heart Failure

BY BRUCE JANCIN

ORLANDO — Heart failure patients who engage in aerobic activity can lower their risk of all-cause mortality or hospitalization, according to a new secondary analysis of data from a major National Heart, Lung, and Blood Institute–sponsored randomized trial.

"It appears that only a modest amount or dose of exercise is needed to potentially improve risk," Dr. Steven J. Keteyian observed in presenting new findings from Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION) at the annual meeting of the American College of Cardiology.

Each 1-metabolic-equivalent-task-hour/week increase in exercise volume in heart failure patients is associated with an additional 5% reduction in risk of all-cause mortality or hospitalization, he reported. The same 1-MET-hour/week increase in exercise volume was also associated with an 11% reduction in the combined secondary end point of cardiovascular death or heart failure hospitalization over a median 2.5-year follow-up. It also conferred a 4.2-meter increase in 6-minute walk distance, a 0.18-mL/kg per minute increase in peak VO_2, and a 0.74-point rise in Kansas City Cardiomyopathy Questionnaire score at 3 months, added Dr. Keteyian, director of the preventive cardiology program at Henry Ford Hospital, Detroit.

Just how much exercise is 1 MET-hour per week? Current guidelines recommend at least 8 MET-hours/week in healthy adults.

The MET-hour/week measure reflects exercise intensity multiplied by duration. For example, a patient who walks at 2 mph for 30 minutes three times per week—a typical regimen in cardiac rehabilitation programs—engages in 3.8 MET-hours/week. If that patient works up to a 40-minute walk at 3 mph five times weekly, that's 9.9 MET-hours/week—and that translates to an estimated further 30% reduction in the risk of all-cause mortality or hospitalization.

HF-ACTION involved 2,331 patients with New York Heart Association class II-IV stable systolic heart failure and an ejection fraction of 35% or less who were randomized to usual care or an aerobic exercise intervention. The program entailed 12 weeks of thrice-weekly 30-minute supervised group exercise sessions at 60%-70% of heart rate reserve, followed by a home program of 40 minutes of exercise at the same intensity five times per week.

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The recently published main results showed a modest 11% reduction in the adjusted relative risk of all-cause mortality or hospitalization in the exercise group (JAMA 2009;301:1439-50). Because adherence to the exercise regimen varied widely, the investigators performed a new dose-response analysis. They restricted it to patients free of death or hospitalization in the first 90 days of the study, reasoning that if exercise had any effects on clinical outcomes, they would not begin to appear until after that point.

The new findings help quantify the benefits of aerobic exercise as a management tool in patients with systolic heart failure, according to Dr. Keteyian.

Discussant Marvin A. Konstam was skeptical in light of the fact that HF-ACTION did not randomize patients to different exercise doses.

"When you define subgroups essentially based upon postrandomization events, you really are losing the value of the randomization process," said Dr. Konstam, professor of medicine at Tufts Medical Center, Boston.

Indeed, it could be argued that the new analysis does not define a dose-response, but instead simply shows that patients who are able to exercise more are going to have better outcomes, he continued.

Dr. Keteyian conceded the limitation but asserted that "the signal is there." ■

moxatag™
(amoxicillin extended-release tablets)
775 mg

The following is a brief summary only; see full Prescribing Information for complete product information.

RX ONLY

INDICATIONS AND USAGE

MOXATAG is a once-daily amoxicillin product indicated for the treatment of tonsillitis and/or pharyngitis secondary to *Streptococcus pyogenes (S. pyogenes)*, more commonly referred to as 'strep throat,' in adults and pediatric patients 12 years or older.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of MOXATAG and other antibacterial drugs, MOXATAG should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria.

DOSAGE AND ADMINISTRATION

The recommended dose of MOXATAG is 775 mg once daily taken within 1 hour of finishing a meal for 10 days. MOXATAG should be taken approximately the same time every day. The full 10-day course of therapy should be completed for effective treatment of tonsillitis and/or pharyngitis secondary to *S. pyogenes*.

Do not chew or crush tablet.

CONTRAINDICATIONS

MOXATAG is contraindicated in patients with known serious hypersensitivity to amoxicillin or to other drugs in the same class or patients who have demonstrated anaphylactic reactions to beta-lactams.

WARNINGS AND PRECAUTIONS

Anaphylaxis and Hypersensitivity Reactions

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients on penicillin therapy. Although anaphylaxis is more frequent following parenteral therapy, it has occurred in patients on oral penicillins. These reactions are more likely to occur in individuals with a history of penicillin hypersensitivity and/or a history of sensitivity to multiple allergens. There have been reports of individuals with a history of penicillin hypersensitivity who have experienced severe reactions when treated with cephalosporins. Before initiating therapy with MOXATAG, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, or other allergens. If an allergic reaction occurs, MOXATAG should be discontinued and appropriate therapy instituted.

***Clostridium difficile* Associated Diarrhea (CDAD)**

Clostridium difficile Associated Diarrhea (CDAD) has been reported with nearly all antibacterial agents, including amoxicillin, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile*.

CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued.

Superinfections

The possibility of superinfections with mycotic or bacterial pathogens should be kept in mind during therapy. If superinfections occur, amoxicillin should be discontinued and appropriate therapy instituted.

Mononucleosis Rash

A high percentage of patients with mononucleosis who receive ampicillin develop an erythematous skin rash. Thus, ampicillin-class antibiotics should not be administered to patients with mononucleosis.

Development of Drug-Resistant Bacteria

Prescribing amoxicillin in the absence of proven or strongly suspected bacterial infection or treating prophylactically is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

False-Positive Urinary Glucose Tests

High urine concentrations of ampicillin may result in false-positive reactions when testing for the presence of glucose in urine using Clinitest®, Benedict's Solution or Fehling's Solution. Since this effect may also occur with amoxicillin, it is recommended that glucose tests based on enzymatic glucose oxidase reactions (such as Clinistix®) be used.

ADVERSE REACTIONS

In a controlled Phase 3 trial, 302 adult and pediatric patients (≥12 years) were treated with MOXATAG 775 mg once-daily for 10 days. The most frequently reported adverse reactions (>1%) which were suspected or probably drug-related are vaginal yeast infection (2.0%), diarrhea (1.7%), nausea (1.3%) and headache (1.0%).

DRUG INTERACTIONS

Probenecid

Probenecid decreases the renal tubular secretion of amoxicillin. Concurrent use of MOXATAG and probenecid may result in increased and prolonged blood levels of amoxicillin.

Other Antibiotics

Chloramphenicol, macrolides, sulfonamides, and tetracyclines may interfere with the bacterial effects of penicillin. This has been demonstrated *in vitro*; however, the clinical significance of this interaction is not well documented.

Oral Contraceptives

As with other antibiotics, amoxicillin may affect the gut flora, leading to lower estrogen reabsorption and potentially resulting in reduced efficacy of combined oral estrogen/progesterone contraceptives.

USE IN SPECIFIC POPULATIONS

Pregnancy: Teratogenic Effects. Pregnancy Category B.

Reproduction studies have been performed in mice and rats at doses up to 2000 mg/kg (12.5 and 25 times the human dose in mg/m^2) and have revealed no evidence of impaired fertility or harm to the fetus due to amoxicillin. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery

It is not known whether use of amoxicillin in humans during labor or delivery has immediate or delayed adverse effects on the fetus, prolongs the duration of labor, or increases the likelihood that forceps delivery or other obstetrical intervention or resuscitation of the newborn will be necessary.

Nursing Mothers

Penicillins have been shown to be excreted in human milk. Amoxicillin use by nursing mothers may lead to sensitization of infants. Caution should be exercised when amoxicillin is administered to a nursing woman.

Pediatric Use

The safety and effectiveness of MOXATAG in pediatric patients 12 years of age and older have been established based on results of a clinical trial that included adults and pediatric patients (12 years or older). The safety and effectiveness of MOXATAG in pediatric patients younger than 12 years has not been established.

Geriatric Use

This drug is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

Renal Impairment

MOXATAG has not been studied in patients with renal impairment; however, a reduction of amoxicillin dose is generally recommended for patients with severe renal impairment. Therefore, MOXATAG is not recommended for use in patients with severe renal impairment (CrCl <30 mL/min) or patients on hemodialysis.

OVERDOSAGE

In case of overdose, discontinue medication, treat symptomatically, and institute supportive measures as required. If the overdose is very recent and there is no contraindication, an attempt at emesis or other means of removal of drug from the stomach may be performed.

Interstitial nephritis resulting in oliguric renal failure has been reported in a small number of patients after overdosage with amoxicillin.

Crystalluria, in some cases leading to renal failure, has also been reported after amoxicillin overdosage in adult and pediatric patients.

Renal impairment appears to be reversible with cessation of drug administration. High blood levels may occur more readily in patients with impaired renal function because of decreased renal clearance of amoxicillin.

For additional information about overdose treatment, call a poison control center (1-800-222-1222).

HOW SUPPLIED/STORAGE AND HANDLING

MOXATAG tablets for oral administration are provided as blue film-coated, oval-shaped tablets that contain 775 mg of amoxicillin. The tablets are printed with "MB-111" on one side in black edible ink. MOXATAG is packaged in bottles as follows:

Presentation	NDC Code
Bottles of 30	11042-142-03

Storage

Store at 25° C (77° F); excursions permitted to 15–30° C (59–86° F) [See USP Controlled Room Temperature.]

MiddleBrook PHARMACEUTICALS®
Germantown, Maryland 20876 USA

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