

Obesity at Age 18 Found to Increase PsA Risk

BY MARY ANN MOON

FROM ARCHIVES OF DERMATOLOGY

People who are obese at age 18 may be at an increased risk for psoriatic arthritis later in life, according to a new report in the July issue of the Archives of Dermatology.

In a single-center study of 943 psoriasis patients, those who reported being obese at age 18 were three times more likely to develop psoriatic arthritis (PsA), compared with patients who reported having a normal body mass index at age 18, reported Dr. Razieh Soltani-Arabshahi and associates of the University of Utah School of Medicine, Salt Lake City.

In a previous study, the researchers found that patients with psoriasis had an increased BMI, compared with controls. So, they "set out to study if obesity increases the risk of PsA," using data from a large cohort of subjects enrolled in the Utah Psoriasis Initiative, the researchers noted.

Patients who had been overweight or obese at age 18 were more likely to report having severe psoriasis than patients who were of normal weight at age 18.

The cohort included consecutive patients older than 18 years who attended university-affiliated psoriasis clinics in 2002-2008 and provided detailed demographic and clinical data.

A total of 250 (27%) of the 943 subjects included in the study reported having PsA.

Of the study patients, 14% had been overweight and 5% had been obese at age 18, according to self-reported height and weight measurements.

Higher BMI was associated with an increased risk of developing PsA, independent of other risk factors such as nail involvement. Each unit increase in BMI at age 18 corresponded to a 5% increase in risk of PsA.

In addition, patients who were obese at age 18 showed an earlier onset of PsA, compared with patients of normal weight at age 18. Twenty percent of those who had been overweight or obese at 18 years developed PsA by age 35. In comparison, among patients of normal

weight at age 18, 20% did not develop PsA until age 48.

Moreover, patients who had been overweight or obese at age 18 were more likely to report having severe psoriasis (47% and 57%, respectively) than patients who were of normal weight at age 18 (39%).

The design of the study did not permit the investigators to infer causality. However, it is plausible that obesity and its associated inflammatory state might contribute to both psoriasis and PsA, Dr. Soltani-Arabshahi and colleagues reported (Arch. Dermatol. 2010;146:721-6).

"Evaluation of additional sample sets in an attempt to replicate these results is imperative for strong conclusions to be drawn," they noted.

The study was limited in that it relied on subjects' self-report of height and weight earlier in life, self-report of psoriasis severity, and self-report of diagnosis of PsA. ■

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In the all-exposure population, the rate of malignancies remained consistent (1.10 events per 100 patient-years) with the rate observed in the 6-month controlled period [see Warnings and Precautions].

Other Adverse Reactions

Adverse reactions occurring in 2% or more of patients on 4 mg/kg or 8 mg/kg ACTEMRA plus DMARD, and at least 1% greater than that observed in patients on placebo plus DMARD, are summarized in Table 2.

Table 2 Adverse Reactions Occurring in at Least 2% or More of Patients on 4 mg/kg or 8 mg/kg ACTEMRA plus DMARD and at Least 1% Greater Than That Observed in Patients on Placebo plus DMARD

Preferred Term	6-Month Phase III Controlled Study Population				
	ACTEMRA 8 mg/kg Monotherapy N = 288 (%)	Methotrexate N = 284 (%)	ACTEMRA 4 mg/kg + DMARDs N = 774 (%)	ACTEMRA 8 mg/kg + DMARDs N = 1582 (%)	Placebo + DMARDs N = 1170 (%)
Upper Respiratory Tract Infection	7	5	6	8	6
Nasopharyngitis	7	6	4	6	4
Headache	7	2	6	5	3
Hypertension	6	2	4	4	3
ALT increased	6	4	3	3	1
Dizziness	3	1	2	3	2
Bronchitis	3	2	4	3	3
Rash	2	1	4	3	1
Mouth Ulceration	2	2	1	2	1
Abdominal Pain Upper	2	2	3	3	2
Gastritis	1	2	1	2	1
Transaminase increased	1	5	2	2	1

DRUG INTERACTIONS

Other Drugs for Treatment of Rheumatoid Arthritis

Population pharmacokinetic analyses did not detect any effect of methotrexate, nonsteroidal anti-inflammatory drugs or corticosteroids on tocilizumab clearance.

Concomitant administration of a single dose of 10 mg/kg ACTEMRA with 10-25 mg MTX once weekly had no clinically significant effect on MTX exposure.

ACTEMRA has not been studied in combination with biological DMARDs such as TNF antagonists [see Dosage and Administration].

Interactions with CYP450 Substrates

In vivo studies with omeprazole, metabolized by CYP2C19 and CYP3A4, and simvastatin, metabolized by CYP3A4, showed up to a 28% and 57% decrease in exposure one week following a single dose of ACTEMRA, respectively. The effect of tocilizumab on CYP enzymes may be clinically relevant for CYP450 substrates with narrow therapeutic index, where the dose is individually adjusted. Upon initiation or discontinuation of ACTEMRA, in patients being treated with these types of medicinal products, therapeutic monitoring of effect (eg, warfarin) or drug concentration (eg, cyclosporine or theophylline) should be performed and the individual dose of the medicinal product adjusted as needed. Prescribers should exercise caution when ACTEMRA is coadministered with CYP3A4 substrate drugs where decrease in effectiveness is undesirable, eg, oral contraceptives, lovastatin, atorvastatin, etc. The effect of tocilizumab on CYP450 enzyme activity may persist for several weeks after stopping therapy.

Live Vaccines

Live vaccines should not be given concurrently with ACTEMRA [see Warnings and Precautions].

USE IN SPECIFIC POPULATIONS

Pregnancy

Teratogenic Effects. Pregnancy Category C. There are no adequate and well-controlled studies in pregnant women. ACTEMRA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

An embryo-fetal developmental toxicity study was performed in which pregnant cynomolgus monkeys were treated intravenously with tocilizumab (daily doses of 2, 10, or 50 mg/kg from gestation day 20-50) during organogenesis. Although there was no evidence for a teratogenic/dysmorphic effect at any dose, tocilizumab produced an increase in the incidence of

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abortion/embryo-fetal death at 10 mg/kg and 50 mg/kg doses (1.25 and 6.25 times the human dose of 8 mg/kg every 4 weeks based on a mg/kg comparison).

Nonteratogenic Effects.

Testing of a murine analogue of tocilizumab in mice did not yield any evidence of harm to offspring during the pre- and postnatal development phase when dosed at 50 mg/kg intravenously with treatment every three days from implantation until day 21 after delivery (weaning). There was no evidence for any functional impairment of the development and behavior, learning ability, immune competence and fertility of the offspring.

Pregnancy Registry:

To monitor the outcomes of pregnant women exposed to ACTEMRA, a pregnancy registry has been established. Physicians are encouraged to register patients and pregnant women are encouraged to register themselves by calling 1-877-311-8972.

Nursing Mothers

It is not known whether tocilizumab is excreted in human milk or absorbed systemically after ingestion. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from ACTEMRA, 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

Safety and effectiveness of ACTEMRA in pediatric patients have not been established.

Geriatric Use

Of the 2644 patients who received ACTEMRA in Studies I to V, a total of 435 rheumatoid arthritis patients were 65 years of age and older, including 50 patients 75 years and older. The frequency of serious infection among subjects treated with ACTEMRA 65 years of age and older was higher than those under the age of 65. As there is a higher incidence in infections in the elderly population in general, caution should be used when treating the elderly.

Hepatic Impairment

The safety and efficacy of ACTEMRA have not been studied in patients with hepatic impairment, including patients with positive HBV and HCV serology [see Warnings and Precautions].

Renal Impairment

No dose adjustment is required in patients with mild renal impairment. ACTEMRA has not been studied in patients with moderate to severe renal impairment.

OVERDOSAGE

There are limited data available on overdoses with ACTEMRA. One case of accidental overdose was reported in which a patient with multiple myeloma received a dose of 40 mg/kg. No adverse drug reactions were observed. No serious adverse drug reactions were observed in healthy volunteers who received single doses of up to 28 mg/kg, although all 5 patients at the highest dose of 28 mg/kg developed dose-limiting neutropenia.

In case of an overdose, it is recommended that the patient be monitored for signs and symptoms of adverse reactions. Patients who develop adverse reactions should receive appropriate symptomatic treatment.

PATIENT COUNSELING INFORMATION

Patient Counseling

Patients should be advised of the potential benefits and risks of ACTEMRA. Physicians should instruct their patients to read the Medication Guide before starting ACTEMRA therapy.

• Infections:

Inform patients that ACTEMRA may lower their resistance to infections. Instruct the patient of the importance of contacting their doctor immediately when symptoms suggesting infection appear in order to assure rapid evaluation and appropriate treatment.

• Gastrointestinal Perforation:

Inform patients that some patients who have been treated with ACTEMRA have had serious side effects in the stomach and intestines. Instruct the patient of the importance of contacting their doctor immediately when symptoms of severe, persistent abdominal pain appear to assure rapid evaluation and appropriate treatment.

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