

Calcium Supplements May Increase CVD Risk

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TORONTO – Calcium supplements appear to cause more harm than good, according to a meta-analysis of 28,000 participants in nine trials that includes a new analysis of more than 16,000 participants in the Women's Health Initiative, but the reanalysis has raised concerns among the WHI's original investigators.

"We calculate that for every 1,000 people treated with calcium for 5 years, it will lead to four additional myocardial infarctions, four additional strokes, and two additional deaths, while preventing three fractures," Dr. Ian R. Reid said.

Major Finding: People taking a calcium supplement showed a statistically significant 24% excess relative risk for MI, a 15% excess relative risk for stroke, and a 16% excess relative risk for MI or stroke.

Data Source: Meta-analysis of nine studies that compared calcium supplements with placebo in a total of more than 28,000 people.

Disclosures: Dr. Reid said that he had no relevant disclosures.

"I don't prescribe calcium supplements to anyone anymore for preventing bone fractures. People should get calcium from their diet," said Dr. Reid of the University of Auckland, New Zealand. He speculated that a calcium supplement, even at a relatively modest dose of 500 mg, produces a "borderline hypercalcemia" that persists for several hours and raises the risk for MI or stroke, the same way that people in the highest quartile for normal blood calcium levels have an increased risk for cardiovascular disease events.

But the researchers who ran the Women's Health Initiative (WHI) study questioned the legitimacy of the new analysis beyond a hypothesis-generating exercise.

"The WHI investigators have concerns about the reanalysis and whether omitting the subgroups with favorable results is appropriate," said Dr. JoAnn E. Manson of Harvard University and Brigham and Women's Hospital, both in Boston, and a WHI coinvestigator.

Dr. Reid and his associates initially reported that calcium supplement use was linked with a statistically significant 27% and 31% relatively in-

creased risk for MI in two separate meta-analyses published online last July (BMJ 2010;341:c3691).

To further explore the impact of calcium supplements on cardiovascular risk, they reanalyzed data collected in a WHI study of more than 36,000 postmenopausal women randomized to receive a daily supplement with 500 mg calcium plus vitamin D or placebo. The original report from the WHI investigators showed that the calcium plus vitamin D did not significantly increase or decrease coronary or cerebrovascular risk in generally healthy postmenopausal women during 7 years of treatment (Circulation 2007;115:846-54).

But at baseline, more than 19,000 (54%) of the women in the study reported using a calcium supplement on their own, and at the end of the study 69% reported the practice, Dr. Reid said. To address the possible confounding, he focused on the 16,718 women in the WHI study who reported not using a personal calcium supplement at entry.



In this subgroup, the MI rates ran 2.5% in women randomized to calcium supplements and 2.0% in the placebo arm, a 22% relative increase that was statistically significant. The rate of MI or stroke ran a relative 16% higher among the women taking calcium, which was also statistically significant. The results showed no significant effect of calcium supplementation on stroke rate, Dr. Reid said.

But if Dr. Reid's analysis did not start with a prior hypothesis, this finding can only be considered hypothesis generating, not hypothesis testing, Dr. Manson said in an interview. "Many subgroups were tested in the WHI, and some would be expected to show significant effect modification by chance," she pointed out.

When data from the WHI subgroup that did not use personal calcium supplements at baseline were added to the meta-analysis, the results showed that those who did take supplements had a 24% relative excess of MIs, a 15% relative excess of stroke, and a 16% relative excess of MI or stroke, Dr. Reid reported. ■

'I don't prescribe calcium supplements to anyone anymore for preventing bone fractures.'

DR. REID

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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/dysmorphogenic 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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