



Arthritis News

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A PROMISING NEW TREATMENT FOR SYSTEMIC SCLEROSIS WELL TOLERATED BY PATIENTS IN INITIAL STUDIES

SAN ANTONIO, TEXAS—A new antibody, still under development, that neutralizes transforming growth factor, TGF β 1, in patients with diffuse cutaneous systemic sclerosis has proven to be well tolerated for the patients who participated in a recent trial, according to research presented this week at the American College of Rheumatology Annual Scientific Meeting in San Antonio, Texas.

Overactivity of TGF β 1, is implicated as a key driver of fibrosis or scarring in many conditions including systemic sclerosis. This chronic rheumatic disease, which causes degenerative changes and scarring in the skin, joints and internal organs, affects approximately one to two individuals in every 10,000, predominantly women (female: male=4:1) between the ages of 30 and 60 years. Those affected experience skin tightness, Raynaud's phenomenon, painful joints and, early in the disease, difficulties in swallowing and gastro-oesophageal reflux.

To study patient tolerance to the future use of CAT-192, an antibody designed to neutralize TGF β 1 and therefore reduce fibrosis, researchers conducted a trial on 45 subjects enrolled in 11 centers in the U.S. and Europe. The patients, all of whom had contracted systemic sclerosis within the past 18 months, were randomly allocated to one of three doses of CAT-192: 10mg/kg, 5mg/kg, 0.5mg/kg or a placebo given by injection on the first day of the study and in weeks six, 12 and 18. Patients were monitored primarily for safety and bodily absorption, distribution, metabolism and excretion of the drug; and secondarily for skin thickness and hardness, overall health assessment, organ-based disease and laboratory test results.

At the end of the study, there was no significant difference in the safety profiles among the different treatment groups. A total of 275 adverse events occurred in 42 of the participants and, of the 13 patients who experienced serious adverse events, two were on placebo. No secondary outcome showed significant change in any of the four treatment groups.

Results indicate that use of CAT 192 in patients with diffuse cutaneous systemic sclerosis was well tolerated in the patients who participated in the trial. In addition, no safety issues were identified in this study. This trial was not powered to determine the efficacy of treatment. No conclusions about the effectiveness of CAT 192 as a therapy can therefore be made at this stage.

“Showing that repeated treatment with an antibody to TGF β 1 appears to be safe in systemic sclerosis is an important first step in the development of treatments that could inhibit this protein in diseases in which overactivity is implicated as a key driver,” said Christopher P. Denton, MD, PhD, Centre for Rheumatology, Royal Free Hospital, London, England, and an investigator in the study.

The American College of Rheumatology is the professional organization for rheumatologists and health professionals who share a dedication to healing, preventing disability and curing arthritis and related rheumatic and musculoskeletal diseases. For more information on the ACR's annual meeting, see www.rheumatology.org/annual.

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Editor's Notes: Dr. Denton will present this research during a scientific session at the ACR Annual Scientific Meeting from 9:00–9:15 AM CT (10:00–10:15 AM ET) on Thursday, October 21, in Room 217 of the Henry B. González Convention Center. He will be available for media questions during a briefing at 1:30 PM CT (2:30 PM ET) on Monday, October 18, in the on-site Press Conference Room, Room 218.

Anti-TGF β 1 Therapy for Diffuse Cutaneous Systemic Sclerosis: a Multicenter, Randomized, Placebo-controlled Phase I/II Trial of CAT-192

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PURPOSE: TGF β overactivity is implicated in systemic sclerosis (SSc) pathogenesis. We report a Phase I/II trial of CAT-192, a human recombinant IgG₄ antibody that neutralizes TGF β 1, in early diffuse cutaneous (dc)SSc.

METHODS: Forty-five subjects within 18 months of SSc onset were enrolled from 11 centers in the USA and Europe and randomly allocated to one of four treatment arms: 10mg/kg, 5mg/kg, 0.5mg/kg or placebo infused on day 0 and weeks 6, 12, and 18. Primary outcomes were safety and pharmacokinetics (PK). Secondary outcomes included modified Rodnan skin score (mRSS), durometer measures of skin hardness, SSc health assessment questionnaire, assessment of organ-based disease, and biomarkers.

RESULTS: The primary end-points were achieved as treatment-related morbidity was undetectable and PK parameters were established. There were 4 deaths, 1 in the 0.5mg/kg and 3 in the 5mg/kg group, none attributable to treatment. Serious adverse events occurred in 13 subjects, including 2 receiving placebo. A total of 275 adverse events occurred in 42 subjects. Biologically active serum levels (>10 μ g/ml) of CAT-192 were confirmed in treatment groups with a half-life (mean \pm se) of 24.0 \pm 2.1 days. No secondary outcome showed significant change among treatment groups. The table summarizes mRSS data throughout the trial. Improvement in mRSS associated significantly with disease duration ($p=0.0008$). TGF β 1 and β 2 mRNA levels were increased in affected (2 fold) and clinically unaffected (1.6 fold) SSc skin ($p=0.011$ and $p=0.002$ respectively) compared with control biopsies. Serum level of N-terminal procollagen peptide (PINP, μ g/L) was greater in SSc (8.5 \pm 3.5) than controls (5.1 \pm 2.4; $n=100$, $p<0.0001$). Although change in PINP correlated with change in skin score ($r=0.37$, $p=0.027$), there was no treatment effect for any biomarker. Levels of soluble IL2 receptor (ng/L) were elevated in SSc (1.8 \pm 0.9) versus controls (0.8 \pm 0.3; $p<0.0001$) and did not change with treatment.

CONCLUSION: Systemic administration of CAT-192 in patients with dcSSc is safe and well tolerated. The study was not powered to determine efficacy, therefore, although mRSS improved more in the 5 or 10 mg/kg subgroups, this may reflect longer disease duration at baseline. Additionally, feasibility of multicenter trials in early dcSSc is confirmed.

		CAT-192 dose (mg/kg)		
Median (range)	Placebo (n=11)	0.5 (n=11)	5 (n=11)	10 (n=10)
Disease duration: Months	5.9 (1, 23)	4.6 (1, 14)	7.2 (1, 17)	9.4 (2, 16)
Baseline mRSS: Units \geq 5	(11, 38)	21 (14, 27)	23 (14, 30)	24 (13, 30)
Change in mRSS: Units	-1 (-12, 9)	3 (-9, 14)	-3 (-10, 12)	-4 (-17, 6)
Percentage of baseline	-4.5 (-60, 31)	14.3 (-64, 70)	-13.0 (-67, 52)	-21.1 (-57, 31)

Disclosure: C.P. Denton, Genzyme 2, 5; P.A. Merkel, Genzyme 2, 5; D.E. Furst, Genzyme 2, 5; D. Khanna, None; P. Emery, Genzyme Corporation 2; V.M. Hsu, None; N. Silliman, Genzyme Corporation 1, 3; J. Streisand, Genzyme Corporation 1, 3; J. Powell, CAT 1, 3; J.H. Korn, Genzyme 2, 5; C.M. Black, Genzyme 2, 5; J.R. Seibold, Genzyme 2, 5

Author disclosure legend—Authors' disclosures of third-party relationships are listed in numeric format according to the following listing:

None—Nothing to disclose; 1—Stock options or bond holdings in a for-profit corporation or self-directed pension plan; 2—Research grants; 3—Employment (full or part-time); 4—Ownership or partnership; 5—Consulting fees or other remuneration (payment); 6—Non-remunerative positions of influence such as officer, board member, trustee or public spokesperson; 7—Receipt of royalties; 8—Speakers bureau.