P528

Assessment of Bone and Cartilage Turnover Markers Following Treatment With Repository Corticotropin Injection in Patients With Persistently Active Rheumatoid Arthritis

Roy Fleischmann,[1] Daniel E. Furst,[2] Erin Connolly-Strong,[3] Jingyu Liu,[3] Julie Zhu,[3] Richard Brasington[4]

[1]University of Texas Southwestern Medical Center, Metroplex Clinical Research Center, Dallas, TX; [2]David Geffen School of Medicine at UCLA, Los Angeles, CA; [3]Mallinckrodt Pharmaceuticals, Bedminster, NJ; [4]Washington University School of Medicine, St. Louis, MO

Introduction

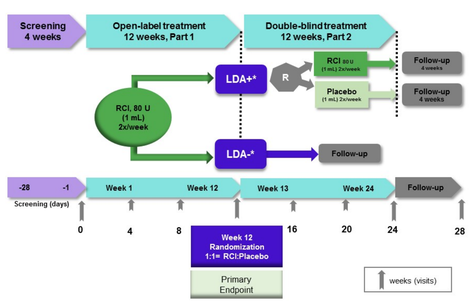
- Persistently active rheumatoid arthritis (RA) is an autoimmune disorder characterized by chronic inflammation and bone loss[1]
- Although short-term administration of corticosteroids is recommended alongside use of disease-modifying anti-rheumatic drugs (DMARDs) for active disease, corticosteroid use is often associated with exacerbation of bone loss[2]
- Repository corticotropin injection (RCI) is approved by the US Food and Drug Administration for short-term adjunctive use in the treatment of RA[3]
- RCI is a naturally sourced complex mixture of purified adrenocorticotropic hormone analogs and other pituitary peptides[3] and acts as an agonist for all 5 melanocortin receptors (MCRs)[4]
- RCI-dependent activation of MCRs exhibits anti-inflammatory and immunomodulatory effects. *In vivo* data have shown RCI-mediated suppression of bone resorption via osteoclast reduction[5]
- As an exploratory aim of a broader 2-part, multicenter, placebo-controlled, phase 4 efficacy and safety study, biomarkers associated with bone loss were assessed to evaluate the impact of RCI treatment on bone turnover in patients with persistently active RA

Methods

Study design

- Adults with persistently active RA despite DMARD and corticosteroid use were enrolled and remained on their current stable DMARD and corticosteroid doses throughout the study (ClinicalTrials.gov ID:NCT02919761)
- During the initial 12-week open-label period (Part 1), all patients received 80 U RCI (subcutaneously [SC], 2x/week) **(Figure 1)**

Figure 1. Study Design



Patients with persistently active rheumatoid arthritis despite treatment with disease-modifying anti-rheumatic drugs and corticosteroids received 12 weeks of open-label treatment with RCI. Responders to RCI treatment were then randomized to placebo or continued RCI treatment for an additional 12 weeks.
Abbreviations: LDA, low disease activity; R, randomization; RCI, repository corticotropin injection.

Methods (cont'd)

- Those who achieved low disease activity (defined as a Disease Activity Score in 28 joints [DAS28] <3.2) at week 12 were subsequently entered into the double-blind period (Part 2) and randomized to RCI (80 U SC 2x/week) or matching placebo for an additional 12 weeks.
- Subjects who did not achieve low disease activity at week 12 were discontinued from further study participation. All subjects had a follow-up visit 28 (±2) days after the last dose of study drug, regardless of treatment group
- Mean levels of bone turnover biomarkers (C-terminal cross-linking telopeptide [CTX], C-terminal cross-linking telopeptide of type I collagen [CTX-I], osteoprotegrin [OPG], N-terminal propeptide of type I collagen [PINP], and soluble receptor activator of nuclear factor kappa-β ligand [sRANKL]) and cartilage degeneration biomarkers (C-terminal cross-linking telopeptide of type II collagen [CTX-II] and CTX-II creatinine [CRT]) were assessed at baseline and at weeks 12 (open-label period) and 24 post-baseline (randomized maintenance period)
- DAS28 scores are also presented, as well as percentages of patients who experienced low disease activity and remission (defined as a DAS28 <2.6) over time

Statistical analyses

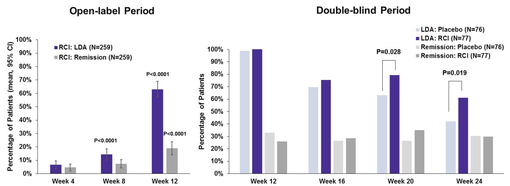
- Statistical analyses were performed on the modified intent-to-treat (mITT) population (all enrolled subjects who received 1 or more doses of study drug and who contributed any efficacy data to the study)
- A one-sample *t* test with a two-sided 95% confidence interval was used to evaluate the change from baseline in the open-label period. Pearson's Chi-square test or a two-sample *t* test with a two-sided 95% confidence interval was used to evaluate the treatment difference in the double-blind randomized maintenance period

Results

Open-label period

- Of the 259 patients entering the open-label period, 163 (62.9%; P<0.0001) achieved low disease activity and 49 (18.9%; P<0.0001) achieved remission by week 12 (**Figure 2**). Improvement in DAS28 is shown in **Figure 3**
- At completion of the open-label period (week 12), most of the bone biomarkers showed no significant change, except for the bone formation marker PINP and cartilage degeneration markers CTX-II and CTX-II CRT, which all significantly decreased (**Table 1**)

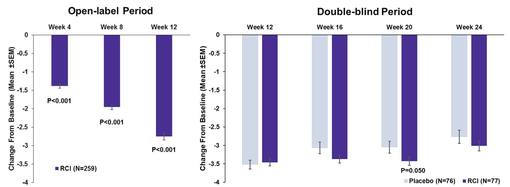
Figure 2. Treatment With RCI: Percentage of Patients Experiencing Low Disease Activity or Remission (mITT Population)



Note: Low disease activity and remission are defined as DAS28 <3.2 and <2.6, respectively. p-values in the open-label period are from one-sample *t* tests comparing baseline and week 12 values. p-values in the double-blind period are from Pearson's Chi-square test comparing RCI and placebo.
Abbreviations: CI, confidence interval; DAS28, Disease Activity Score with 28 joint count; LDA, low disease activity; mITT, modified intent-to-treat; RCI, repository corticotropin injection.

Results (cont'd)

Figure 3. Treatment With RCI: Improvement in DAS28 Scores (mITT Population)



p-values in the open-label period are from one-sample *t* tests comparing baseline and week 12 values. p-values in the double-blind period are from two-sample *t* tests comparing RCI and placebo.
Abbreviations: DAS28, Disease Activity Score with 28 joint count; mITT, modified intent-to-treat; RCI, repository corticotropin injection; SEM, standard error of the mean.

Table 1. Bone and Cartilage Biomarker Levels From the Open-label Period (N=259)

Marker	Mean (SD)	
	Baseline	Week 12
Bone Degeneration		
CTX, µg/L	4.8 (2.1)	4.8 (1.9)
CTX-I, µg/L	0.4 (0.2)	0.4 (0.2)
Bone Formation		
PINP, µg/L	52.2 (28.2)	47.4 (26.2)**
Bone Resorption		
sRANKL, pmol/L	2057.7 (3592.9)	2107.6 (3794.6)
OPG, pmol/L	4.7 (1.8)	4.7 (2.0)
Cartilage Degeneration		
CTX-II, µg/L	3.5 (2.3)	3.0 (2.2)**
CTX-II CRT, ng/mmol	452.4 (325.4)	362.5 (273.1)***

**P<0.01, ***P<0.001 (from a one-sample *t* test, modified intent-to-treat population).
Abbreviations: CRT, creatinine; CTX, C-terminal cross-linking telopeptide; CTX-I, C-terminal cross-linking telopeptide of type I collagen; CTX-II, C-terminal cross-linking telopeptide of type II collagen; OPG, osteoprotegrin; PINP, N-terminal propeptide of type I collagen; SD, standard deviation; sRANKL, soluble receptor activator of nuclear factor kappa-β ligand.

Double-blind randomized maintenance period

- Of the 163 patients who achieved low disease activity in the open-label period, 153 entered the 12-week double-blind maintenance period and were randomized to treatment with RCI (N=77) or placebo (N=76)
- Of the 153 patients who entered the double-blind period, 127 (83%) completed the study
- For those patients in the RCI treatment group, there was a significant increase from baseline in mean sRANKL levels at both week 12 (P=0.036) and week 24 (P=0.010) compared with placebo, suggesting a potential increase in osteoclast differentiation, but all other biomarkers remained stable (**Table 2**)

Results (cont'd)

Table 2. Bone and Cartilage Biomarker Levels in Patients Randomized in the Double-blind Period (RCI vs Placebo)

Marker	Mean (SD)					
	Baseline		Week 12		Week 24	
	Placebo (N=76)	RCI (N=77)	Placebo (N=76)	RCI (N=77)	Placebo (N=76)	RCI (N=77)
Bone Degeneration						
CTX, µg/L	4.6 (2.0)	4.8 (1.9)	4.6 (1.6)	4.6 (1.4)	4.5 (1.7)	4.8 (2.8)
CTX-I, µg/L	0.4 (0.2)	0.4 (0.2)	0.4 (0.2)	0.5 (0.2)	0.4 (0.2)	0.4 (0.2)
Bone Formation						
PINP, µg/L	52.5 (26.4)	54.8 (28.8)	48.7 (25.1)	51.2 (29.1)	53.1 (26.2)	54.3 (40.1)
Bone Resorption						
sRANKL, pmol/L	2416.3 (3825.9)	1519.4 (2378.3)	2358.6 (4401.7)	2451.8 (4417.6)*	2105.6 (4116.9)	2939.0 (5006.2)*
OPG, pmol/L	4.7 (1.8)	4.9 (1.8)	4.7 (1.9)	4.8 (2.2)	5.1 (2.1)	4.9 (2.0)
Cartilage Degeneration						
CTX-II, µg/L	3.6 (2.4)	3.7 (2.5)	3.2 (2.4)	2.9 (2.2)	3.3 (2.1)	3.1 (1.9)
CTX-II CRT, ng/mmol	460.5 (368.3)	463.7 (316.9)	382.5 (257.5)	368.0 (228.6)	391.6 (236.0)	339.4 (189.7)

*P<0.05 (from two-sample *t* test, RCI vs placebo, modified intent-to-treat population).
Abbreviations: CRT, creatinine; CTX, C-terminal cross-linking telopeptide; CTX-I, C-terminal cross-linking telopeptide of type I collagen; CTX-II, C-terminal cross-linking telopeptide of type II collagen; OPG, osteoprotegrin; PINP, N-terminal propeptide of type I collagen; RCI, repository corticotropin injection; SD, standard deviation; sRANKL, soluble receptor activator of nuclear factor kappa-β ligand.

Conclusions

- Overall, bone and cartilage biomarker levels were mostly stable throughout this study of patients with persistently active RA, suggesting that any steroidogenic effects of RCI were minimal
- During the open-label phase, cartilage degeneration markers significantly decreased, suggesting a potential therapeutic effect, whereas bone degradation markers remained stable
- Some evidence of increased osteoclast differentiation in response to RCI was noted during the double-blind phase; however, markers of bone degeneration remained stable, suggesting no significant effect of RCI on bone loss

References

1. Fardellone P, et al. *Mediators Inflamm*. 2014:484280.
2. Tada M, et al. *Osteoporos Int*. 2016;27(2):729-35.
3. Acthar [package insert]. Bedminster, NJ: Mallinckrodt ARD LLC; 2019.
4. Wright D and Fitch R. Acthar® Gel (Repository Corticotropin Injection) enhances remyelination after cuprizone-induced demyelination. Poster Presented at: The Consortium of Multiple Sclerosis Centers Annual Meeting; May 28, 2019; Seattle, WA.
5. Wright D, et al. *Arthritis Rheumatol*. 2018;70(Suppl 9). Abstract 57.

Acknowledgment and Funding

Professional writing and editorial support was provided by MedLogix Communications, LLC, Itasca, Illinois, under the direction of the authors and was funded by Mallinckrodt Pharmaceuticals.

Disclosures

R.F. has received clinical trial grants from AbbVie, Acea, Amgen, AstraZeneca, BMS, Boehringer Ingelheim, Celgene, Genentech, Gilead, GSK, Janssen, Eli Lilly, Merck, Pfizer, Roche, Sanofi, Aventis, Samumed, and UCB. He has received consultancy fees from AbbVie, Acea, Akros, Amgen, BMS, Celltrion, Galvani, Gilead, GSK, Janssen, Eli Lilly, Merck, Novartis, Pfizer, Sandoz, Sanofi Aventis, Taiho, and UCB; **R.B.** has served as a speaker for Amgen, Mallinckrodt Pharmaceuticals, Novartis, and Pfizer; **D.E.F.** has received grants and consultancy fees from AbbVie, Actelion, Amgen, BMS, Corbus, NIH, Novartis, Pfizer, and Roche/Genentech. He has also received consultancy fees from Cytori and speaking fees from CMC Connect (McCann Health Company); **E.C.-S.**, **J.L.**, and **J.Z.** are employees of Mallinckrodt Pharmaceuticals.