Tofacitinib in Patients with Active RA with an Inadequate Response to Tumor Necrosis Factor Inhibitors

Written by Maria Vinall

An oral Janus kinase inhibitor, in combination with methotrexate, led to significant improvements in a treatment-refractory rheumatoid arthritis (RA) population with no significant safety concerns.

In the Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of the Safety and Efficacy of 2 Doses of CP-690,550 In Patients With Active Rheumatoid Arthritis On Background Methotrexate With Inadequate Response to TNF Inhibitors study [ORAL Sync; NCT00960440], 399 participants with active RA, age 54.3 to 55.4 years, and a disease duration of 11 to 13 years, were randomized 2:2:1:1.

- Tofacitinib 5 mg twice daily
- Tofacitinib 10 mg twice daily
- Placebo, advanced to tofacitinib 5 mg twice daily
- Placebo, advanced to tofacitinib 10 mg twice daily

All patients were receiving methotrexate and had failed at least one tumor necrosis factor (TNF) inhibitor, reported lead investigator Gerd-Rüdiger Burmester, MD, Charité-University Medicine, Berlin, Germany. Approximately one-third of subjects (27%) had failed two TNF inhibitors, and 8% had failed three or more. Fourteen percent of patients had discontinued anti-TNF treatment due to intolerance.

Primary study endpoints were ACR20 responder rate, Health Assessment Questionnaire-Disability Index (HAQ-DI) change from baseline, and the rate of patients who achieved a Disease Activity Score 28 (DAS28) erythrocyte sedimentation rate (ESR) <2.6 at Month 3.

At 3 months, the ACR20 rate increased 41.7% in the 5-mg group and 48.1% in the 10-mg group compared with 24.4% in the placebo groups ($p<0.05$ and $p<0.0001$, respectively; Table 1). Statistically significant improvements also occurred in ACR 50 and 70 rates at Month 3 and in all indicators at 6 months. The mean change in the HAQ at 3 months was -0.43% in ($p<0.0001$; Table 1). Approximately 10% of patients in the 10-mg group achieved remission.

Table 1.

	Tofacitinib 5 mg BID (n=133)	Tofacitinim 10 mg BID (n=134)	PBO (n=132)	PBO to tofacitinib 5 mg BID (n=66)	PBO to tofacitinib 10 mg BID (n=66)
Efficacy					
ACR20† (%) (Month 3[a])	41.7*	48.1***	24.4	NA	NA
ACR20† (%) (Month 6)	51.5***	54.9***	NA	45.5***	40.0***
ACR50† (%) (Month 3)	26.5***	27.8***	8.4	NA	NA
ACR50† (%) (Month 6)	37.1***	30.1***	NA	28.79***	20.0***
ACR70† (%) (Month 3)	13.6***	10.5***	1.5	NA	NA
ACR70† (%) (Month 6)	15.9***	15.8***	NA	10.6*	9.2*
Mean change HAQ-DI‡ (Month 3[a])	-0.43***	-0.46***	-0.18	NA	NA
Mean change HAQ-DI‡ (Month 6)	-0.51***	-0.50***	NA	-0.54***	-0.38***
DAS28-4 (ESR) <2.6† (%) (Month 3[a])	6.7*	11.2*	1.7	NA	NA
DAS28-4 (ESR) <2.6† (%) (Month 6)	10.7*	15.8*	NA	11.1*	3.3
Mean change DAS28-4 (ESR) (Month 3)	-1.9***	-2.1***	-0.9	NA	NA
Mean change DAS28-4 (ESR) (Month 6)	-2.4*	-2.7***	NA	-2.3*	-2.1
Safety, n (%)					
AEs (Months 0-3)	71 (53.4)	76 (56.7)	75 (56.8)	NA	NA
AEs (Months 3-6)	57 (42.9)	58 (43.3)	NA	24 (36.4)	28 (42.4)
SAEs (Months 0-3)	2 (1.5)	2 (1.5)	6 (4.5)	NA	NA
SAEs (Months 3-6)	5 (3.8)	6 (4.5)	NA	3 (4.5)	2 (3.0)
D/C (AEs) (Months 0-6)	12 (9.0)	13 (9.7)	7 (5.3)	1 (1.5)	2 (3.0)

a=primary enpoints; †=non-responder imputation; ‡=mixed-effect longitudinal linear model; *p<0.05; ***p<0.0001 vs PBO (Month 3)/vs baseline (Month 6); D/C=discontinuation; SAE=serious adverse event; PBO=placebo..

There were also statistically significant improvements in the DAS28-4 (ESR) at 3 months, with a mean change of -1.9% and -2.1% in the 5-mg and 10-mg groups, respectively, and -2.4% and -2.7% at 6 months.

Adverse events (AE) were generally mild—primarily infections—with no significant differences between groups. At 3 months, 1.5% of the study drug group experienced serious AEs compared with 4.5% in the placebo group. One patient who was taking the 10-mg BID dose of tofacitinib, a 51-year-old woman with a prior history of obesity and hypertension who was also taking hormone replacement therapy, died during the study from a pulmonary embolism. The death was judged by the study investigator to be unrelated to the study medication.

Less than 1% of participants were lost to follow up, while 9% and 10% of the study drug groups discontinued the trial because of adverse effects versus 5% of the placebo group.

This was the first Phase 3 study of tofacitinib in combination with methotrexate in patients with active RA who responded inadequately to TNF inhibitors. In this patient population, tofacitinib demonstrated rapid, significant, and clinically meaningful improvements in the signs and symptoms of RA, physical function, and disease activity.

Long-Term Safety and Efficacy of Denosumab in Postmenopausal Osteoporosis

Written by Debra Gordon, MS

The efficacy and safety of the antiresorptive agent denosumab on bone mineral density (BMD) and fracture rates were assessed in an open-label extension, crossover trial of the original 3-year, randomized, placebo-controlled Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months study. [FREEDOM; NCT00089791; Cummings SR et al. *N Engl J Med* 2009].

Subjects were recruited for the 3-year extension of the trial if they had completed their Year 3 and had not missed more than 1 dose of the study medication (or placebo) during the trial. Of 5928 individuals who were eligible for the extension, 4550 (77%) elected to continue—2343 continued to receive denosumab and 2207 crossed over from placebo to denosumab. All participants received 60 mg of denosumab every 6 months, took supplemental calcium and vitamin D daily, and will be followed for 7 years in the extension—therefore, up to 10 years of treatment with denosumab.

Lead investigator Jacques Brown, MD, CHUQ-CHUL Research Centre, Laval University, Laval, Quebec, Canada, noted that both groups demonstrated a rapid and profound reduction of the resorption marker serum collagen type 1 crosslinked C-telopeptide (CTX) and a similar improvement in levels of the bone formation marker serum type 1 procollagen N-terminal (P1NP) after infusion, with the characteristic attenuation observed at the end of each dosing period.

Participants in the extension phase exhibited continued improvement in BMD. There was a 6-year mean cumulative improvement of 15.2% at the lumbar spine and 7.5% at the total hip. The crossover group experienced a statistically significant ($p<0.05$) increase in BMD of 9.4% at the lumbar spine and 4.8% at the total hip, increases that were comparable with the denosumab-treated group during the initial 3-year FREEDOM trial.

The annual rate of new vertebral and nonvertebral fractures in the long-term group remained low (Table 1). In the crossover group, the rate of vertebral and nonvertebral fractures was much lower than in the placebo group of FREEDOM.

Adverse events per 100 subject years were similar between the crossover and extension groups. Two participants in the crossover group developed osteonecrosis of the jaw (ONJ), both of which resolved. Two participants in the follow-on group also developed ONJ, and both continue to be followed. There have been no reported atypical femur fractures in either group.

Table 1. Annual Rate of New Vertebral and Nonvertebral Fractures.

FREEDOM			
New Fractures	**Year 1**	**Year 2**	**Year 3**
Vertebral	2.2%	3.1%	3.1%
Nonvertebral	3.1%	2.9%	2.5%
Extension Group			
New Fractures	**Year 4**	**Year 5**	**Year 6**
Vertebral	1.4%		1.1%
Nonvertebral	1.4%	1.5%	1.6%
Crossover Group			
New Fractures	**Year 4**	**Year 5**	**Year 6**
Vertebral	0.9%		1.5%
Nonvertebral	2.4%	1.8%	1.7%

"The continued increase in bone mineral density was surprising," said Prof. Brown. "With an antiresorptive, we would expect at some point that bone mineral density would plateau; so, it is very surprising to still see a significant increase over 6 years," he concluded.