Safety and efficacy of upadacitinib in patients with active rheumatoid arthritis refractory to biologic disease-modifying anti-rheumatic drugs (SELECT-BEYOND): a double-blind, randomised controlled phase 3 trial

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RobotReviewer report

Risk of bias table

trial	design	n	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment
Genovese MC, 2018	RCT	?? ?	+	+	+	+

Population	1. Patients were aged 18 years or older, diagnosed with rheumatoid arthritis for at least 3 months before enrolment, and fulfilled the 2010 American College of Rheumatology (ACR) and European League Against Rheumatism classification criteria for rheumatoid arthritis. 2. The ORAL-STEP study was done in patients who had inadequate response or intolerance to at least one anti-TNF drug, and compared twice-daily tofacitinib at 5 mg or 10 mg with placebo for 3 months, followed by twice-daily tofacitinib 5 mg or 10 mg for 3 months, on a background of methotrexate. 3. Main exclusion criteria were previous exposure to a JAK inhibitor or a history of inflammatory joint diseases other than rheumatoid arthritis.
Intervention	1. The ORAL-STEP study was done in patients who had inadequate response or intolerance to at least one anti-TNF drug, and compared twice-daily tofacitinib at 5 mg or 10 mg with placebo for 3 months, followed by twice-daily tofacitinib 5 mg or 10 mg for 3 months, on a background of methotrexate. 2. Randomisation and masking We randomly assigned patients (2:2:1:1) in a doubleblinded manner to either receive upadacitinib 15 mg or upadacitinib 30 mg, or to receive placebo for 12 weeks followed by upadacitinib 15 mg or upadacitinib 30 mg from week 12 onwards in a blinded extension for up to 5 years (appendix). 3. 20 Patients continued stable csDMARD therapy for the first 24 weeks of the study, restricted to oral or parenteral methotrexate (7¬∑5,Äì25¬∑0 mg per week), chloroquine (‚â§250 mg per day), hydroxychloroquine (‚â§400 mg per day), sulfasalazine (‚â§3000 mg per day), or leflunomide (‚â§20 mg per day).
Outcomes	1. Key secondary endpoints assessed at week 12 were the proportions of patients who achieved 50% or 70% improvement in ACR criteria (ACR50 or ACR70); changes

		from baseline in DAS28(CRP); health assessment questionnaire‚Äìdisability index (HAQ-DI); short form 36 (SF-36) physical component summary (PCS); and the See Online for appendix Articles proportion of patients achieving ACR20 at week 1. 2. Additional secondary endpoints, measured at all visits up to week 12, included the indi vidual components of the ACR response (HAQ-DI, TJC68, SJC66, physician's global assessment of disease activity [GA], patient's GA, pain, and hsCRP concentration); the proportions of patients who had low disease activity, defined as clinical disease activity index (CDAI) of 10 or less or simplified disease activity index (SDAI) of 11 or less; an improvement from baseline in HAQ-DI of 0@BULLET22 or more, defined as the minimal clinically important difference; and change from baseline in morning stiffness duration and severity. 3. Efficacy, patient-reported outcomes, laboratory assessments , adverse event assessments, local urine pregnancy tests, vital signs, height, and weight were measured at weeks 1, 2, 4, 8, 12, 16, and 20.
Bias	**Judgement**	**Support for judgement**
Random sequence generation	low	1. Randomisation and masking We randomly assigned patients (2:2:1:1) in a doubleblinded manner to either receive upadacitinib 15 mg or upadacitinib 30 mg, or to receive placebo for 12 weeks followed by upadacitinib 15 mg or upadacitinib 30 mg from week 12 onwards in a blinded extension for up to 5 years (appendix). 2. Randomisation at baseline was performed using interactive response technology and a schedule generated by the data sciences department at AbbVie. 3. 20 Patients continued stable csDMARD therapy for the first 24 weeks of the study, restricted to oral or parenteral methotrexate (7¬∑5‚Äì25¬∑0 mg per week), chloroquine (‚â§250 mg per day), hydroxychloroquine (‚â§400 mg per day), sulfasalazine (‚â§3000 mg per day), or leflunomide (‚â§20 mg per day).
Allocation concealment	low	1. Patients, investigators, and the funder were masked to allocation. 2. 499 patients were randomly assigned (n=165 upadacitinib 15 mg; n=165 upadacitinib 30 mg; n=85 placebo then upadacitinib 15 mg; and n=84 placebo then upadacitinib 30 mg) and one patient withdrew from the upadacitinib 15 mg group before the start of study treatment because of accidental randomisation. 3. The placebo and study drug were identical in appearance.
Blinding of participants and personnel	low	1. Patients, investigators, and the funder were masked to allocation. 2. The placebo and study drug were identical in appearance. 3. Methods Study design and participants SELECT-BEYOND is a double-blind, randomised controlled phase 3 trial with a 12-week placebo-controlled period followed by a double-blind extension of up to 5 years.
Blinding of outcome assessment	low	1. The ORAL-STEP study was done in patients who had inadequate response or intolerance to at least one anti-TNF drug, and compared twice-daily tofacitinib at 5 mg or 10 mg with placebo for 3 months, followed by twice-daily tofacitinib 5 mg or 10 mg for 3 months, on a background of methotrexate. 2. Herpes zoster occurred in more patients in the upadacitinib 30 mg group than in the other groups in the first 12 weeks; during weeks 12‚Äì24, two cases of herpes zoster were reported in each of the groups receiving were mild, and all except one involved a single dermatome. 3. Patients, investigators, and the funder were masked to allocation.