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ORIGINAL ARTICLE

Dupilumab Efficacy and Safety in Moderate-to-Severe Uncontrolled Asthma

M. Castro, J. Corren, I.D. Pavord, J. Maspero, S. Wenzel, K.F. Rabe, W.W. Busse, L. Ford, L. Sher, J.M. FitzGerald, C. Katelaris, Y. Tohda, B. Zhang, H. Staudinger, G. Pirozzi, N. Amin, M. Ruddy, B. Akinlade, A. Khan, J. Chao, R. Martincova, N.M.H. Graham, J.D. Hamilton, B.N. Swanson, N. Stahl, G.D. Yancopoulos, and A. Teper

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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
Castro M, 2018	RCT	?? ?	+	+	+	+

Characteristics of studies

Castro M, 2018

Population	1. We randomly assigned 1902 patients 12 years of age or older with uncontrolled asthma in a 2:2:1:1 ratio to receive add-on subcutaneous dupilumab at a dose of 200 or 300 mg every 2 weeks or matched-volume placebos for 52 weeks. 2. Patients Patients 12 years of age or older with physiciandiagnosed persistent asthma for 12 months or more, according to the Global Initiative for Asthma 2014 guidelines
Interventio n	1. A Quick Interventions and Procedures Patients were randomly assigned (in a 2:2:1:1 ratio) to receive 52 weeks of add-on therapy with subcutaneous dupilumab at a dose of 200 mg (loading dose, 400 mg) or 300 mg (loading dose, 600 mg) every 2 weeks or a matched-volume placebo (1.14 ml or 2.00 ml, respectively) for each active dose

	(supplied in prefilled syringes). 2. We randomly assigned 1902 patients 12 years of age or older with uncontrolled asthma in a 2:2:1:1 ratio to receive add-on subcutaneous dupilumab at a dose of 200 or 300 mg every 2 weeks or matched-volume placebos for 52 weeks. 3. Blood eosinophilia occurred after the start of the intervention in 52 patients (4.1%) who received dupilumab as compared with 4 patients (0.6%) who received placebo.
Outcomes	1. The primary efficacy end points were the annualized rate of severe exacerbation events (number of severe exacerbations per patient-year) during the 52-week intervention period and the absolute change from baseline in the FEV 1 before bronchodilator use at week 12 in the overall trial population. 2. The primary end points were the annualized rate of severe asthma exacerbations and the absolute change from baseline to week 12 in the forced expiratory volume in 1 second (FEV 1) before bronchodilator use in the overall trial population. 3. 18 The incidence of adverse events and serious adverse events that emerged during the trial period was reported, with the trial period defined as the time from the first administration of the trial regimen to the last administration of the trial regimen plus 98 days or until the patient enters the extension study.

Bias	Judgement	Support for judgement
Random sequence generation	low	1. A Quick Interventions and Procedures Patients were randomly assigned (in a 2:2:1:1 ratio) to receive 52 weeks of add-on therapy with subcutaneous dupilumab at a dose of 200 mg (loading dose, 400 mg) or 300 mg (loading dose, 600 mg) every 2 weeks or a matched-volume placebo (1.14 ml or 2.00 ml, respectively) for each active dose (supplied in prefilled syringes). 2. We randomly assigned 1902 patients 12 years of age or older with uncontrolled asthma in a 2:2:1:1 ratio to receive add-on subcutaneous dupilumab at a dose of 200 or 300 mg every 2 weeks or matched-volume placebos for 52 weeks. 3. Patients completed a screening period of 4 weeks (window, ¬±1 week), followed by randomization to subcutaneous injections of dupilumab or matched-volume placebo , a 52-week randomized intervention period, and a 12-week postintervention follow-up period (Fig.
Allocation concealment	low	1. A Quick Interventions and Procedures Patients were randomly assigned (in a 2:2:1:1 ratio) to receive 52 weeks of add-on therapy with subcutaneous dupilumab at a dose of 200 mg (loading dose, 400 mg) or 300 mg (loading dose, 600 mg) every 2 weeks or a matched-volume placebo (1.14 ml or 2.00 ml, respectively) for each active dose (supplied in prefilled syringes). 2. An independent data and safety monitoring committee conducted blinded monitoring of patient safety data (details on the committee are available in the Supplementary Appendix). 3. Randomization was conducted by means of interactive voice,ÄìWeb response technology and was stratified according to age (<18 years or ,â•18 years), peripheral-blood eosinophil count (<300 or ,â•300 per cubic millimeter) at screening, inhaled glucocorticoid dose (medium or high), and country.
Blinding of participants and personnel	low	1. A Quick Interventions and Procedures Patients were randomly assigned (in a 2:2:1:1 ratio) to receive 52 weeks of add-on therapy with subcutaneous dupilumab at a dose of 200 mg (loading dose, 400 mg) or 300 mg (loading dose, 600 mg) every 2 weeks or a matched-volume placebo (1.14 ml or 2.00 ml, respectively) for each active dose (supplied in prefilled syringes).

		2. This randomized, double-blind, placebo-controlled , parallel-group trial assessed the efficacy of dupilumab in patients with uncontrolled moderate-to-severe asthma. 3. The annualized rate of severe asthma exacerbations was 0.46 (95% confidence interval [CI], 0.39 to 0.53) among patients assigned to 200 mg of dupilumab every 2 weeks and 0.87 (95% CI, 0.72 to 1.05) among those assigned to a matched placebo, for a 47.7% lower rate with dupilumab than with placebo (P<0.001); similar results were seen with the dupilumab dose of 300 mg every 2 weeks.
Blinding of outcome assessment	low	1. Patients who discontinued the assigned intervention were encouraged to return to the clinic for all remaining trial visits, and all severe exacerbations up to week 52 were included in the primary analysis, regardless of whether the patient was receiving an intervention . 2. An independent data and safety monitoring committee conducted blinded monitoring of patient safety data (details on the committee are available in the Supplementary Appendix). 3. Data were collected by the investigators and analyzed by the sponsors.