



Journal club

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DUPILUMAB IN MODERATE-TO-SEVERE ASTHMA: GOOD OUTCOMES IN CHILDREN

Dupilumab, a monoclonal antibody that blocks interleukin 4 (IL-4) and interleukin 13 (IL-13), the principal mediators of inflammation in children with asthma, is now approved for treatment of asthma in adults and adolescents. As part of the Liberty Asthma VOYAGE trial, Bacharier *et al* assessed the efficacy and safety of dupilumab administered every 2 weeks (<30 kg=100 mg subcutaneously (SC), >30 kg=200 mg SC) in children aged 6–11 years with moderate-to-severe asthma (*N Engl J Med* 2021; DOI:10.1056/NEJMoa2106567). They randomised 408 children with moderate-to-severe asthma (dupilumab, n=273; placebo, n=135) and split into two primary efficacy populations: type 2 inflammatory asthma (blood eosinophils ≥ 150 cells/mm³ or FE_{NO} ≥ 20 ppb) and patients with blood eosinophils ≥ 300 cells/mm³. All patients receiving dupilumab had significantly lower rates of severe exacerbations (relative risk 0.46, 95% CI 0.31 to 0.67) than the placebo group, were more likely to remain exacerbation free and had fewer courses of systemic glucocorticoids. The dupilumab group also had greater improvement in predicted prebronchodilator FEV₁ (least-squares mean difference 4.7, 95% CI 1.9 to 7.5) and greater improvement in Asthma Control Questionnaire (ACQ-7) scores (least-squares mean difference -0.28, 95% CI -0.44 to -0.12). In the population studied, dupilumab had an acceptable adverse event profile with safety findings similar to those in adult and adolescent patients.

DUPILUMAB IN MODERATE-TO-SEVERE ASTHMA: BENEFITS PERSIST LONG TERM IN ADULTS AND ADOLESCENTS

Dupilumab has shown good outcomes in clinical trials of patients with uncontrolled asthma for up to 1 year. In the TRAVERSE study, Wechsler *et al* (*Lancet Respir Med* 2022;10:11) assessed the safety and efficacy of dupilumab (300 mg subcutaneously every 2 weeks) for 96 weeks in adults and adolescents previously completing a dupilumab asthma study (n=2282 recruited of 2302 eligible participants). Patients from both placebo and dupilumab treatment arms of parent studies were eligible. A subgroup of patients with a type 2 inflammatory phenotype (eosinophils ≥ 150 cells/ μ L or FE_{NO} ≥ 25 ppb) that previously received dupilumab were followed up for 148 weeks (n=364). Long-term dupilumab exposure was well tolerated with the number

of treatment-emergent adverse events similar to parent trials and only rarely led to drug discontinuation (2%–6%; 1–4 patients per 100 patient-years). On continued dupilumab treatment, improvements in FEV₁ were sustained at 96 weeks, with rapid improvements noted in patients who had previously received placebo. Sustained improvements were also observed in asthma control (measured by Asthma Control Questionnaire 5) and health-related quality-of-life (measured by Asthma Quality of Life Questionnaire). In patients followed up for 148 weeks, dupilumab continued to demonstrate good efficacy with sustained reduction in annualised exacerbation rates and prebronchodilator FEV₁ improvement. Of the 2055 non-oral corticosteroid-dependent patients, 157 (7.6%) developed antidrug antibodies (ADAs) and 77 (3.7%) had pre-existing ADAs. ADA status had no clinically significant impact. Overall, the improvements previously described following dupilumab treatment appear to be sustained in adults and adolescents with moderate-to-severe asthma post 1 year of treatment.

REDUCING ORAL CORTICOSTEROIDS FOLLOWING BENRALIZUMAB INITIATION IN ADULTS WITH SEVERE ASTHMA: CAN BE DONE QUICKER THAN YOU THINK

Many people with severe asthma require oral corticosteroids (OCS) for symptom control, but this therapy is associated with systemic side effects and adrenal suppression. Biologics offer an alternative method of achieving asthma control in these patients allowing reduction/cessation of OCS; however, there is currently no consensus on how best to approach OCS reduction. In the PONENTE trial, Menzies-Gow *et al* (*Lancet Respir Med* 2022;10:47) evaluate the use of a personalised algorithm for rapid OCS reduction and adrenal function monitoring in patients with severe asthma following benralizumab initiation. Patients on maintenance OCS (n=598; mean age 53 years, 25% <18 years; 64% women; 81% white) were commenced on benralizumab 30 mg subcutaneously and given a personalised OCS reduction plan according to their baseline OCS dose and adrenal function status. OCS reduction started following their second injection at 4 weeks. Following this algorithm, 62.88% (95% CI 58.86 to 66.76) of patients eliminated daily OCS use and 81.94% (95% CI 78.62 to 84.94) achieved either elimination of OCS or a dosage of ≤ 5 mg where further reduction was stopped due to adrenal insufficiency. On initial testing, 60% of patients had adrenal insufficiency. On follow-up testing, 34% with complete adrenal insufficiency had recovered to normal/partial insufficiency and 37% with partial insufficiency recovered to

normal levels. During reduction, there were no reports of adrenal crisis or adverse events related to adrenal insufficiency. Despite rapid reduction in daily OCS, benralizumab was still associated with improved asthma control and a reduction in exacerbation frequency.

SHORT-ACTING B₂-AGONIST PRESCRIPTIONS IN ASTHMA: MORE PRESCRIPTIONS AND OVER-RELIANCE ASSOCIATED WITH WORSE CLINICAL OUTCOMES

The National Review of Asthma Deaths in the UK found an association between underuse of inhaled corticosteroids (ICS) and excessive use of short-acting β_2 -agonists (SABAs) with death. Although guidelines recommend ICS as management for mild asthma, many patients are still prescribed SABA monotherapy. Those with controlled/partially controlled asthma should not require >2 SABA doses/week (equates to <2 SABA canisters/year). In the SABINA III study, Bateman *et al* (*Eur Respir J* 2021; DOI:10.1183/13993003.01402-2021) evaluated prescriptions and over-the-counter purchases of SABA among patients with asthma aged ≥ 12 years attending primary and specialist care across 24 countries across 5 continents. Of the 8351 patients recruited (primary care, n=1440, specialist care, n=6872), 38% were prescribed ≥ 3 SABA canisters/year (45.8% of mild asthmatics). SABA monotherapy was prescribed in a small proportion of mostly mild patients (5.1%). Of the 58% patients prescribed maintenance therapy and SABA, 61.7% were prescribed ≥ 3 and an astounding 29.3% ≥ 10 SABA canisters/year. Prescription of >2 SABA canisters/year was associated with higher severe exacerbation rates (adjusted incident rate 1.40–1.92, with higher rates with more SABA use) and worse asthma control (adjusted OR for having at least partly controlled asthma 0.64–0.33). This study echoes earlier work in the UK and Italy, demonstrating an association of high SABA prescriptions with poor asthma outcomes, and suggests missed opportunities to optimise asthma control with appropriate maintenance treatment.

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