Indirect comparison of efficacy of dupilumab *versus* mepolizumab and omalizumab for severe type 2 asthma

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To the Editor:

Recently, several biologics have been introduced as add-on treatment for severe asthma [1]. The biologics target the underlying mechanism driving the disease and are recommended for specific phenotypes such as mepolizumab (anti-interleukin (IL)-5) for severe eosinophilic asthma [2] and omalizumab (anti-immunoglobulin (Ig)E) for severe allergic asthma [3]; *i.e.* specific endotypes of type 2 inflammation. Dupilumab (anti-IL-4Rα) is a newer biologic recommended for severe asthma with type 2 inflammation characterised by elevated blood eosinophils (⩾150 per µL) and/or exhaled nitric oxide fraction (F_{eNO} ⩾25 ppb) [4]. Due to the IL-4Rα activity of dupilumab it is likely to inhibit two type 2 inflammatory pathways and, therefore, a patient can be eligible for more than one of the biologics, which is challenging in practice as no previous study has compared the efficacy of dupilumab with mepolizumab and omalizumab.

The aim of this study was to compare the efficacy of dupilumab with mepolizumab and omalizumab in patients aged >12 years with severe type 2 asthma. Therefore, a predefined protocol was developed by an expert committee under the Danish Medicines Council, where two PICO questions were defined: "What is the safety and efficacy of dupilumab compared to mepolizumab?" and "What is the efficacy and safety of dupilumab compared to omalizumab?"

Outcomes were predefined as critical (exacerbations leading to a course of oral corticosteroids (OCS), emergency department visit or hospital admission, or reduction in maintenance OCS treatment) or important and a minimal clinically important difference (MCID) was predefined for each outcome. Dupilumab was compared with mepolizumab and omalizumab for eight outcomes: 1) reduction of annual exacerbations; 2) patients not experiencing exacerbations; 3) lung function measured by forced expiratory volume in 1 s (FEV_1); 4) patients achieving an improvement in FEV_1 ⩾200 mL; 5) asthma control measured with an Asthma Control Questionnaire; 6) quality of life measured with an Asthma Quality of Life Questionnaire; 7) incidence of serious adverse events (SAEs); and 8) specific subtypes of SAEs. Furthermore, dupilumab was compared with mepolizumab for three additional outcomes: OCS dosage reduction; patients able to eliminate OCS treatment; and patients with a reduction in OCS dosage of ⩾50%.

A systematic literature review finalised during September 2019 identified 436 publications of which 33 based on 23 clinical studies were included. Three studies compared dupilumab with placebo [5–9], four compared mepolizumab with placebo, and 16 compared omalizumab with placebo or an active comparator. The initial literature search and analyses were done by Sanofi (Copenhagen, Denmark) and subsequently validated by the expert committee and the secretariat of the Danish Medicines Council.

Indirect comparisons were performed according to Bucher's method. In the comparison of dupilumab with mepolizumab for severe eosinophilic asthma, we included dupilumab studies with a prespecified subgroup analysis on patients with blood eosinophils ⩾150 per µL. This was possible in DRI12544 [6, 9] and QUEST [5, 7], but not in the VENTURE study [8]. Three comparisons were made to investigate the effect on outcomes: A: severe eosinophilic asthma, 24–32 weeks treatment; B: severe eosinophilic asthma, 52 weeks treatment; and C: OCS dependent severe eosinophilic asthma, 24 weeks treatment.

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This indirect comparison of dupilumab, mepolizumab and omalizumab for patients with severe type 2 asthma fulfilling start-up criteria for more than one drug shows no significant efficacy differences https://bit.ly/3pK9Nf9

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TABLE 1 Results of indirect comparisons using Bucher's test for dupilumab *versus* mepolizumab and dupilumap *versus* omalizumab for treatment of severe type 2 asthma

Outcome	Unit of measurement	MCID	Dupilumab[#] *versus* mepolizumab[¶]		Dupilumab *versus* omalizumab[+]	
			Difference in absolute values (95% CI)	Difference in relative value (95% CI)	Difference in absolute values (95% CI)	Difference in relative value (95% CI)
Exacerbation rate	Mean reduction of annual exacerbations, n	0.5 exacerbation per year	B: −0.19 (−0.53–0.32), p=0.39	B: 0.85 (0.57–1.26), p=0.43	B: −0.11 (−0.27–0.11), p=0.26	B: 0.85 (0.61–1.17), p=0.33
	Percentage of patients without exacerbations	10%	B: −10.6 (−21.9–4.5), p=0.12	B: 0.80 (0.60–1.08), p=0.14	B: 2.6 (−5.6; 12.2), p=0.58	B: 1.05 (0.90–1.21), p=0.53
OCS maintenance treatment	Mean % reduction of daily OCS dose	20% (at least 2.5 mg prednisolone equivalent)				
	Percentage of patients able to eliminate daily OCS treatment	5%	C: −0.5 (−9.9–27.6), p=0.94	C: 0.97 (0.31–2.91), p=0.96		
	Percentage of patients with a reduction of OCS daily dose⩾50%	10%	C: −1.4 (−21.0–29.9), p=0.92	C: 0.97 (0.61–1.57), p=0.91		
Lung function, FEV_1	Mean difference in FEV_1	200 mL	A: +100 (13–188), p=0.025 B: +189 (62–316), p=0.004 C: +106 (−122–334), p=0.37		B: +96 (11–182), p=0.028	
	Percentage of patients who achieved an improvement in FEV_1 ⩾200 mL	15%				
ACQ	Mean difference in ACQ	0.5	A: −0.02 (−0.22–0.18), p=0.86 C: 0.05 (−0.41–0.51), p=0.84		A: −0.11 (−0.42–0.20), p=0.50	
AQLQ	Mean difference in AQLQ	0.5	A: −0.13 (−0.32–0.06), p=0.18 C: −0.01 (−0.41–0.40), p=0.96		A: −0.08 (−0.30–0.15), p=0.50	
SAEs	Total incidence of SAEs	5%	A: 6.5 (−1.6–27.5), p=0.39 B: 2.0 (−5.7–17.6), p=0.75 C: 26.0 (1.5–257.1), p=0.013	A: 1.97 (0.76–5.13), p=0.16 B: 1.15 (0.57–2.35), p=0.71 C: 19.55 (2.10–184.6), p=0.009	A: 3.0 (−1.8–14.9), p=0.49 B: 0.2 (−2.7–5.3), p=0.93	A: 1.61 (0.64–4.05), p=0.32 B: 1.04 (0.60–1.80), p=0.90
	Specific subtypes of SAEs, *e.g.* anaphylaxis		No analysis	No analysis		

All estimates are for dupilumab compared to mepolizumab and omalizumab. MCID: minimal clinically important difference; OCS: oral corticosteroids; FEV_1: forced expiratory volume in 1 s; ACQ: Asthma Control Questionnaire; AQLQ: Asthma quality of life Questionnaire; SAE: serious adverse events. A: severe asthma, 24–32 weeks treatment; B: severe asthma, 48–52 weeks treatment; C: OCS-dependent asthma, 24 weeks treatment. [#]: dupilumab studies: [10–14]; [¶]: mepolizumab studies: [15–18]; [+]: omalizumab studies: [19–40].

In the comparison of dupilumab with omalizumab for severe allergic asthma, we included dupilumab studies with subgroup analysis defined by total IgE ⩾30 IU·mL^{-1}, perennial inhalant allergy, and one of the following: blood eosinophils ⩾150 per µL or F_{eNO} ⩾25 ppb. Two comparisons were made as there were no omalizumab trials in OCS dependent asthma: A: severe allergic asthma, 20–32 weeks treatment; and B: severe allergic asthma, 48–52 weeks treatment.

Apart from lung function and SAEs, we found no significant differences for the predefined critical or important clinical outcomes in the comparisons between dupilumab and mepolizumab. We found an absolute mean difference in FEV_1 of +100 mL (95% CI 13–188) at 24 weeks and +189 mL (62–316) at 52 weeks in favour of dupilumab. While both were significant, neither were above the prespecified MCID of 200 mL and no differences were observed for OCS dependent asthma. We found a significant increase in the proportion of SAEs in OCS dependent severe eosinophilic asthma at 24 weeks of treatment with an absolute difference of 26.0% (1.5–257.1) and relative difference of 19.5% (2.1–184.6) in favour of mepolizumab, which was above the MCID of 5% difference, but not significant in the non-OCS dependent groups (table 1). The risk of bias in the included studies assessed by the Cochrane risk of bias tool revealed some concerns due to selection bias. The overall quality of evidence assessed by GRADE was considered low.

In the comparisons between dupilumab and omalizumab only lung function showed significant results with an absolute mean difference in FEV_1 of +96 mL (11–182) at 48–52 weeks of treatment, which was below the prespecified MCID (table 1). The Cochrane risk of bias tool revealed some risk of bias due to incomplete descriptions in the included studies. Furthermore, the general quality of evidence assessed by GRADE was considered very low, due to low comparability of the studies.

These indirect comparisons of dupilumab *versus* mepolizumab and omalizumab treatment for severe type 2 asthma revealed no differences of clinical importance, except for an increase in SAEs in favour of mepolizumab among OCS dependent asthmatics although with a very wide confidence interval. Unfortunately, no head-to-head studies of biologics for severe type 2 asthma have been published and therefore our results are based on indirect comparisons of studies with varying population characteristics, inconsistency, and imprecise outcome definitions. Thus, the quality of the generated evidence is estimated to be low, but still presents the best comparison to date. Furthermore, the risk of bias in the omalizumab studies was considered high due to unclear methods and poor presentation of risk of bias. However, in the mepolizumab studies the risk of bias was in general considered low and in the dupilumab studies there was also a low risk of bias although there were some concerns regarding selection bias. For now, there is no evidence supporting that one of the investigated biologics is superior to another in patients eligible for more than one biologic, although dupilumab seems to have a better effect on lung function but may result in more SAEs. Furthermore, it is unknown whether specific subtypes of type 2 asthma will benefit more from dupilumab, mepolizumab or omalizumab.

In conclusion, by using indirect comparisons we found no clinically significant differences in efficacy outcomes between dupilumab, mepolizumab and omalizumab in patients aged >12 years with severe type 2 asthma characterised by eosinophilia and/or perennial allergy. Randomised controlled head-to-head comparisons of biologics for severe type 2 asthma are needed to aid treatment decisions.

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