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LETTER

Safety of combining biologics in severe asthma: Asthma-related and unrelated combinations

To the Editor,

Monotherapies with antibodies approved for severe asthma treatment were reported to be safe, with side effects close to placebo[1]. However, the safety of concomitant treatments with several biologics in asthma is poorly understood. Two scenarios for treatment with two or more biologics in asthma exist. Firstly, patients may receive an additional biologic approved for severe asthma, either to treat insufficiently controlled typical co-morbidities, or as an add-on treatment for insufficiently controlled asthma. Secondly, patients may receive another biologic not approved for asthma for the treatment of an unrelated disease. Concomitant treatment with 2 immunomodulating antibodies is approved in oncologic diseases such as melanoma [2] or mesothelioma [3]; however, possible autoimmune toxicities remain a concern. In rheumatoid arthritis or inflammatory bowel diseases, concomitant treatment with two or more biologics is currently avoided, because of concerns related to serious infections [4,5]. In contrast, the safety of concomitant treatments with two or more biologics in asthma is unclear. There was no safety signal (but also no additive efficacy) in a trial investigating concomitant treatment with the anti-interleukin 4 receptor antibody dupilumab and the anti-interleukin 33 antibody itepekimab [6]. However, despite several single case reports [7–10], there are no larger case series investigating this issue.

Therefore, seven German academic severe asthma centres (Rostock, Hannover, Mainz/Heidelberg, Berlin, Magdeburg, Kiel, Munich) were asked to report all severe asthma cases documented in their databases with a concomitant treatment (for at least 3 months) with two or more biologics. In order to minimise biases, there were no other specific inclusion or exclusion criteria (for instance, clinical efficacy of dual therapy was not a criterion, to exclude a healthy survivor effect). Patients with a smoking history of more than 10 pack years were also included, because these patients can have typical type 2 marker profiles and are often candidates for a treatment with biologics in real life [11]. A total of 25 patients (15 women, 10 men; median age: 54 years) were identified (Tables 1 and 2). Fifteen patients concomitantly received 2 biologics approved for asthma: 8 were treated for co-morbidities such as CRSwNP, atopic dermatitis, urticaria or EGPA, while 7 received treatment for a combined action on asthma control (Group A, Table 1). In all 15 cases, a switch to another biologic (as a monotherapy) was evaluated or done before starting the dual therapy. The other 10 patients received one biologic for asthma treatment and another (not approved for asthma treatment) for an unrelated disease (Group B, Table 2). The median duration of dual treatment (time point: February 2022) was 9 months (3–38 months) in group A and 24 months (6–49 months) in group B. In Group A, the dual treatment was stopped in 4 patients: in all cases, this was done because of clinical ineffectiveness, not because of adverse effects (Table 1, Non-Responders). All other patients continue to receive two or three biologics concomitantly, with currently no reported adverse effects during this treatment (time point: February 2022).

Taken together, our case series confirms evidence from several single case reports [7–10] and a recent clinical trial [6] that a dual therapy with biologics involving at least one biologic approved for asthma treatment appears to be safe in patients with severe asthma. The safety of the anti-TSLP antibody tezepelumab (which reduces all type 2 biomarkers by blocking TSLP, a target upstream of the inflammatory cascade) may serve as an additional clue for the safety of treatments with several antibodies targeting downstream mediators in severe asthma [12]. These findings are in contrast to dual immunomodulatory treatments in cancer [2,3], rheumatoid arthritis and inflammatory bowel diseases [4,5], where the initiation of a second (approved) biologic was associated with an increased risk for autoimmune toxicities or serious infections. Despite the small number, our data provide preliminary reassurance for clinicians treating patients with severe asthma, that, as far as safety and biologics approved for asthma treatment are concerned, a treatment with an additional biologic can be considered safe in specific, well-documented cases. However, patients need to be informed that safety data are still very limited and that prospective, larger and longer data collections are needed to come to a more robust recommendation.

Hendrik Suhling, Thomas Bahmer, Klaus F. Rabe and Katrin Milger are Members of the German Center for Lung Research (DZL).

TABLE 1 Group A

Pt	Age	Sex	AO	PY	All	Biol 1	Indic 1	Biol 2	Indic 2	Mo	AE	Ex	OU	ACT Bef	ACT Last	FEV1% Bef	FEV1% Last
Responder																	
1	70	F	Adult	0	+	Ben	SA	Dup	AD	9	–	N	N	8	17	83	108
2	32	F	Adult	0	–	Ben	SA	Dup	CRS	9	–	N	N	25	25	108	105
3	49	M	Early	0	+	Dup	SA CRS	Mep	SA	6	–	N	N	19	25	31	32
4	52	M	Adult	10	–	Ben	SA	Oma	CsU	11	–	N	R	20	17	47	79
5	26	F	Adult	0	–	Ben	SA EGPA	Dup	CRS	25	–	N	R	15	20	87	112
6	83	F	Early	0	+	Oma	SA	Mep	EGPA	14	–	N	R	13	18	72	72
7	52	F	Adult	0	+	Mep	SA	Dup	CRS NERD	3	–	N	N	21	25	80	86
8	39	M	Adult	3	–	Ben	SA	Dup	CR	4	–	N	N	14	20	88	99
9	44	M	Adult	0	+	Mep	SA	Dup	AD	36	–	N	N	13	17	63	68
10	48	M	Early	0	+	Oma	SA	Mep	SA	38	–	R	N	6	18	23	46
11	56	F	Adult	0	+	Oma	SA NERD	Dup	SA NERD	18	–	R	R	14	21	24	57
Non-Responder																	
12	54	M	Early	0	+	Mep	SA	Oma	SA	11	–	U	U	6		59	
						Ben	SA			6					7		68
13	41	F	Early	0	+	Oma	SA	Dup	SA AD	5	–	U	U	7	8	89	90
14	55	M	Adult	15	–	Ben	SA EGPA	Dup	SA	6	–	U	U	5	7	28	32
15	25	F	Early	0	+	Oma	SA FA	Mep	SA	9	–	U	U	16		31	
								Res	SA	6					16		28

Note: Shown are patients (Pt) treated with 2 biologics approved for the treatment of asthma. The table displays the age of asthma onset (AO), number of pack years (PY), presence of a history of allergies (All), the first (1) biologic (Biol) given to the patient (initially as a monotherapy) and its indication (Indic), and the second (2) biologic (added to the first biologic) and its indication, the duration of dual biologic treatment in months (Mo), the occurrence of adverse effects (AE: denotes no AE reported). Shown are effects of the dual biologic treatment on asthma exacerbations (Ex)(N: no exacerbations anymore, R: reduced exacerbation rate and U: unchanged exacerbation rate), on oral corticosteroid use (OU)(N: no oral corticosteroid use anymore, R: reduced oral corticosteroid use and U: unchanged oral corticosteroid use), on asthma control (as measured with the asthma control test, ACT) and lung function (as measured with the forced expiratory volume in the first second, FEV_1, in % of the predicted value), before (Bef) and during dual treatment (the last available value is shown: Last). Patients were grouped according to the clinical response regarding exacerbation rates and oral corticosteroid use (11 Responder, 4 Non-Responder). The patients with EGPA received concomitant immunosuppressive treatment (azathioprine and/or oral corticosteroids). *Biologics:* Benralizumab (Ben), Dupilumab (Dup), Mepolizumab (Mep), Omalizumab (Oma), Reslizumab (Res). *Indications*: Atopic dermatitis (AD), Chronic rhinosinusitis with nasal polyps (CRS), Chronic spontaneous urticaria (CsU), Eosinophilic granulomatosis with polyangiitis (EGPA), Food allergy (FA), Non-steroidal anti-inflammatory drug exacerbated respiratory disease (NERD) and Severe Asthma (SA).

TABLE 2 Group B

Pt	Age	Sex	AO	PY	All	Biol 1	Indic 1	Biol 2 (3)	Indic 2 (3)	Mo	AE	Ex	OU	ACT Bef	ACT Last	FEV_1% Bef	FEV_1% Last
16	70	F	Adult	5	-	Eta	PA	Ben	SA	25	-	N	N	11	11	43	61
17	40	F	Adult	1	+	Eta	AS	Dup	SA	36	-	N	N	20	18	85	81
18	58	M	Adult	5	-	Ved	UC	Dup	SA	26	-	N	N	13	25	60	82
19	66	F	Adult	0	-	Mep	SA	Rit	RA	24	-	N	N	16	19	89	99
20	66	F	Adult	0	-	Ben	SA	Eta	RA	33	-	N	R	15	25	35	78
21	54	M	Adult	12	+	Mep	SA	Ust	CD	6		U	N	10	8	38	33
22	44	F	Early	3	+	Ben	SA	Rit	EGPA	6	-	R	N	10	14	71	80
								(Den)	(OP)	(18)	-						
23	57	F	Early	0	+	Can	TRAPS	Dup	SA	24	-	R	R	9	14	19	39
								(Ali)	(HC)	(18)	-						
24	60	F	Adult	2	-	Ben	SA	Den	OP	18	-	N	N	14	21	63	96
25	63	M	Adult	0	+	Dup	SA	Bro	PA	16	-	N	R	12	17	90	94

Note: Shown are patients (Pt) treated with one biologic approved for asthma treatment and another biologic not approved for asthma treatment. The table displays the age of asthma onset (AO), number of pack years (PY), presence of a history of allergies (All), the first (1) biologic (Biol) given to the patient (initially as a monotherapy) and its indication (Indic), and the second (2) biologic (added to the first biologic) and eventually a concomitant third (3) biologic and its indication, the duration of dual biologic treatment in months (Mo), the occurrence of adverse effects (AE: denotes no AE reported). Shown are effects of the dual biologic treatment on asthma exacerbations (Ex)(N: no exacerbations anymore, R: reduced exacerbation rate and U: unchanged exacerbation rate), on oral corticosteroid use (OU)(N: no oral corticosteroid use anymore, R: reduced oral corticosteroid use and U: unchanged oral corticosteroid use), on asthma control (as measured with the asthma control test, ACT) and lung function (as measured with the forced expiratory volume in the first second, FEV_1, in % of the predicted value), before (Bef) and during dual treatment (the last available value is shown: Last). *Biologics:* Alirocumab (Ali), Benralizumab (Ben), Brodalumab (Bro), Canakinumab (Can), Denosumab (Den), Dupilumab (Dup), Etanercept (Eta), Mepolizumab (Mep), Rituximab (Rit), Ustekinumab (Ust), Vedolizumab (Ved), *Indications*: Ankylosing spondylitis (AS), Crohn's disease (CD), Hypercholesterinemia (HC), Osteoporosis (OP), Psoriasis arthritis (PA), Rheumatoid arthritis (RA), Severe Asthma (SA), TNF receptor-associated periodic syndrome (TRAPS) and Ulcerative colitis (UC).

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PATIENT CONSENT STATEMENT

Informed consent for anonymous publication of the data was obtained from the participants.

Marek Lommatzsch[1]
Hendrik Suhling[2]
Stephanie Korn[3]
Karl-Christian Bergmann[4]
Jens Schreiber[5]
Thomas Bahmer[6]
Klaus F. Rabe[7]
Roland Buhl[8]
Johann Christian Virchow[1]
Katrin Milger[9]

[1]*Department of Pneumology and Critical Care Medicine, University of Rostock, Rostock, Germany*
[2]*Department of Respiratory Medicine, Hannover Medical School, Hannover, Germany*
[3]*IKF Pneumologie, Mainz, Germany and Department of Pneumology and Respiratory Care Medicine, University of Heidelberg, Heidelberg, Germany*
[4]*Institute of Allergology, Charité, Universitätsmedizin Berlin and Fraunhofer Institute for Translational Medicine and Pharmacology, Allergology and Immunology, Berlin, Germany*
[5]*Department of Pneumonology, University Hospital, Otto-Von-Guericke-University, Magdeburg, Germany*
[6]*University Hospital Schleswig-Holstein, Campus Kiel, Internal Medicine Department I, Kiel, Germany*
[7]*LungenClinic Grosshansdorf, Grosshansdorf, Germany and University Hospital Schleswig-Holstein-Campus Kiel, Department for Internal Medicine I, Kiel, Germany*
[8]*Pulmonary Department, Mainz University Hospital, Mainz, Germany*
[9]*Department of Medicine V, University Hospital, LMU Munich, and Helmholtz Center Munich, Munich, Germany*

Correspondence
Marek Lommatzsch, Abteilung für Pneumologie und Internistische Intensivmedizin, Universitätsmedizin Rostock, Ernst-Heydemann-Str. 6, 18057 Rostock, Germany.
Email: marek.lommatzsch@med.uni-rostock.de

ORCID

Marek Lommatzsch https://orcid.org/0000-0002-9305-9348
Hendrik Suhling https://orcid.org/0000-0002-8197-5314
Katrin Milger https://orcid.org/0000-0003-2914-8773

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