As-needed low-dose inhaled corticosteroid/formoterol therapy in patients with severe asthma included in the German Asthma Net cohort

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To the Editor:

Asthma is a chronic inflammatory airway disease with variable airway obstruction as well as bronchial hyperreactivity [1]. With a 12-month prevalence between 1.8% and 6.4%, asthma causes a high economic burden in Germany [2, 3]. The German Asthma Net (GAN), a nonprofit organisation, was founded in 2009 with the aim of establishing a central, prospective patient registry to contribute to research and public health in the field of severe bronchial asthma (Global Initiative for Asthma (GINA) steps IV and V). Up to the end of December 2022, data from 3504 patients has been entailed, which represents the comprehensive cohort of patients with severe asthma in German-speaking countries.

Short-acting β_2-agonists (SABA) have played a pivotal role and been widespread in asthma therapy for decades until GINA changed the recommendation in 2019 to use inhaled corticosteroids (ICS) for all levels of disease severity, regularly or whenever needed [4]. Many studies reported overuse of SABA therapy, which is associated with higher rates of exacerbations and poor disease control [4–6]. Real-world data about changes in asthma therapy after the GINA update, and the comparison of clinical parameters between SABA reliever-based regimens and single-inhaler corticosteroid ICS/formoterol maintenance and reliever therapy (SMART or MART) in patients with severe asthma and patients with monoclonal antibody therapy are barely available. Consequently, we analysed the use of SABA reliever-based regimens and ICS/formoterol SMART regimens before the update of the GINA recommendation (2019 and earlier) and in the years after, complemented by a comparison of clinical parameters and lung function between those two therapeutic approaches.

Exacerbation was defined as use of oral corticosteroids (OCS) for ⩾3 days, doubling the OCS dose already prescribed or hospitalisation, and asthma control was detected by the Asthma Control Questionnaire (ACQ), Asthma Control Test (ACT) [7] and GINA control status [8]. Additionally, data on lung function and laboratory parameters were analysed. All patients gave informed consent to use their anonymised data [9]. The “SABA” group included all registered patients with therapy that included on-demand fenoterol, salbutamol or terbutaline, and the “SMART” group, all patients with fixed-combination ICS/formoterol as maintenance and reliever therapy. Patients with combined treatment with SABA and SMART were excluded. Documented prescriptions per patient for each year were analysed for 2019–2022; for the period before 2019, the patients’ last documented visit was considered. When comparing SABA and SMART, the last documented visit with each therapy was evaluated.

The statistical analyses for the comparison between treatments were performed using the Mann–Whitney U-test for continuous and Chi-squared test for categorial variables (SAS version 9.4, TS1M6). Categorical variables were summarised as the number of patients and percentages. Continuous variables were summarised using descriptive statistics (mean and 95% confidence interval).

Time-dependent analysis of the proportions of the therapy groups showed that before 2019, a SABA therapy was given in 64% and a SMART therapy in 1%; after the GINA update in 2022, these proportions became 48% and 12%, respectively (table 1). To our knowledge, detailed analyses of the use of SABA and SMART before and after changes in the GINA guidelines in a large cohort are still missing. With the aid of the SABINA (SABA Use in Asthma) programme, (over)use of SABA was still detected not only in

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After the GINA update in 2019, the proportion of SMART therapy increased with evidence for better disease control in SMART patients compared to SABA alone https://bit.ly/3SSPX1C

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TABLE 1 Asthma treatment before and after the update in the Global Initiative for Asthma (GINA) guideline

	Before	After			
	<2019[#]	2019	2020	2021	2022
Patients	1273	1283	1389	1489	1188
SABA	817 (64%)	734 (57%)	751 (54%)	774 (52%)	575 (48%)
SMART	14 (1%)	41 (3%)	85 (6%)	145 (10%)	137 (12%)
Biologics	665 (52%)	843 (66%)	967 (70%)	1038 (70%)	800 (67%)
ICS single inhaler	244 (19%)	192 (15%)	209 (15%)	211 (14%)	169 (14%)
ICS/LABA	1030 (81%)	1108 (87%)	1168 (84%)	1209 (81%)	935 (79%)
ICS/LABA/LAMA		4 (<1%)	35 (3%)	97 (7%)	109 (9%)
LTRA	438 (34%)	385 (30%)	396 (29%)	371 (25%)	270 (23%)
Theophylline	158 (12%)	88 (7%)	76 (5%)	58 (4%)	30 (3%)
Missing data	440 (35%)	506 (39%)	540 (39%)	556 (37%)	466 (39%)

Comparison of characteristics and parameters between patients treated with SABA and SMART reliever treatment in the total cohort	**SABA**	**SMART**	**p-value**
Patients	2008	252	
Age, years	56 (46–64)	56 (47–65)	0.5681
Females	1152 (59%)	127 (50%)	0.012
Smoking history, pack-years	10 (3.2–20)	12.5 (3.8–26.3)	0.0781
Exacerbations in the past 12 months			0.00012
0	885 (45%)	144 (57%)	
1	296 (14.9%)	39 (15.5%)	
>1	710 (36%)	66 (26%)	
GINA control status			<0.00012
Controlled	538 (26.8%)	139 (55.4%)	
Partly controlled	590 (29.4%)	66 (26.3%)	
Uncontrolled	878 (43.8%)	46 (18.3%)	
ACQ score[¶]	2.4 (1.2–3.6)	1 (0.2–2.7)	<0.00011
ACT score	17 (11–22)	20 (16–24)	<0.00011
FEV_1, % pred	71 (54–86)	74 (59–89)	0.00461
FVC, % pred	85 (71–97)	89 (77–101)	0.00031
$MEF_{25\%}$, % pred	46 (27–74)	55 (35–78)	0.01131
RV, % pred	132 (109–162)	122 (99–147)	0.00031
P_{O_2}, mmHg	74 (68–80)	82 (72–88)	0.00011
Eosinophils, per µL	160 (60–398)	170 (70–400)	0.69601
F_{ENO}, ppb	33 (17–57)	29 (16–55)	0.761
Systemic steroids	589 (29%)	32 (13%)	<0.00012
Prednisolone-equivalent dose, mg	7.5 (5–17.5)	5 (3.9–12.5)	0.1283
ICS single inhaler	330 (16%)	8 (3%)	<0.00012
ICS/LABA	1670 (83%)	222 (88%)	0.04582
ICS/LABA/LAMA	87 (4%)	21 (8%)	0.41152
LTRA	616 (31%)	33 (13%)	<0.00012
Theophylline	158 (8%)	4 (2%)	0.00032
Biologic therapy	1217 (61%)	164 (65%)	0.16992

Comparison between patients treated with SABA and SMART reliever treatment in the biologic cohort	**SABA**	**SMART**	**p-value**
Patients	1217	164	
GINA control status			<0.0001[+]
Controlled	427 (35%)	103 (63%)	
Partly controlled	384 (32%)	37 (23%)	
Uncontrolled	405 (33%)	24 (15%)	
ACQ score[¶]	1.8 (0.8–3.2)	0.8 (0–2)	<0.0001[§]
ACT score	19 (14–23)	21 (16–24)	0.0006[§]
FEV_1, % pred	74 (58–88)	73 (57–89)	0.763[§]
FVC, % pred	89 (75–100)	89 (77–99)	0.703[§]
RV, % pred	129 (106–156)	123 (98–147)	0.067[§]
F_{ENO}, ppb	33 (18–53)	28 (17–55)	0.774
Systemic steroids	319 (26%)	24 (15%)	0.001[+]
Prednisolone-equivalent dose, mg	5 (5–10)	5 (4–12)	0.4934

Continued

TABLE 1 Continued

Comparison between patients treated with SABA and SMART reliever treatment in the biologic cohort	SABA	SMART	p-value
ICS single inhaler	186 (15%)	7 (4%)	0.001[+]
ICS/LABA	1025 (84%)	146 (89%)	0.108[+]
ICS/LABA/LAMA	40 (3%)	10 (6%)	0.484[+]
LTRA	352 (29%)	21 (13%)	<0.0001[+]
Theophylline	90 (7%)	1 (<1%)	0.001[+]

Data are presented as n, n (%) or median (interquartile range), unless otherwise stated. SABA: short-acting β_2-agonist; SMART: single-inhaler maintenance and reliever therapy; ICS: inhaled corticosteroid; LABA: long-acting β_2-agonist; LAMA: long-acting muscarinic antagonist; LTRA: leukotriene receptor antagonist; ACQ: Asthma Control Questionnaire; ACT: Asthma Control Test; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; $MEF_{25\%}$: maximum expiratory flow at 25% FVC; RV: residual volume; P_{O_2}: oxygen tension; F_{ENO}: exhaled nitric oxide fraction. [#]: if a patient had more than one visit in the period before 2019, only the last visit was counted; [¶]: on a scale of 0–6 points; [+]: Chi-squared test; [§]: Mann–Whitney U-test.

Germany but also in other European countries even after changes in the GINA guidelines independent of the treatment step [10]. For Germany, our data demonstrate decreasing use (table 1). However, nearly half of the included patients in our cohort still used SABA. This may be related to the comparatively small number of approved preparations for SMART, and the variety of monotherapy, combination therapy and triple therapy. In addition, patient habituation to a specific inhaler as on-demand therapy complicates changes, potentially explaining the steadily growing but still low proportion of SMART.

Intergroup analysis revealed more men in the SMART group but no significant differences in regard to smoking status (pack-years) or age (table 1). Further comparative analyses revealed better asthma control, indicated by GINA control status, lower ACQ scores, less exacerbation and higher ACT scores in the SMART group. Concerning lung function parameters, patients under SMART exhibited higher forced expiratory volume in 1 s, forced vital capacity (FVC), maximum expiratory flow at 25% FVC and lower residual volume compared to patients with SABA therapy, with no significant differences in other lung function parameters (data not shown). Moreover, blood eosinophil counts and exhaled nitric oxide fractions did not differ significantly, whereas blood gas analysis revealed significantly higher oxygen tension (table 1). As presented in table 1, in a more in-depth analysis, a comparison of patients with monoclonal antibody therapy demonstrated better disease control, shown by ACT, ACQ and GINA control status, as well as less steroid requirement, without significant differences in lung function, for SMART. Of note, there were no differences in the distribution of antibody use between groups (data not shown). Concerning other therapies, the use of leukotriene receptor antagonists, theophylline and ICS monotherapy were more often observed in SABA group, but not that of ICS/long-acting β_2-agonist (LABA)/long-acting muscarinic antagonist. In the SMART group, the use of ICS/LABA as basic inhaled therapy tended to be more frequent in all included patients, with no differences in patients with additional biologic therapy.

To date, several studies and meta-analyses have evaluated the differences in clinical outcome between SMART and therapy strategies containing SABA at various stages of disease severity and, thus, different therapy steps [11–14]. Due to the great proportion of patients with antibody therapy, here, we were first able to compare SMART and SABA therapy in this particular patient cohort, providing valuable information about a potential benefit in patients with severe asthma (GINA step V). The results of the aforementioned studies were only based on data for budesonide/formoterol, whereas our study also included data on other ICS/formoterol combinations.

Generally, asthma patients throughout all treatment steps and, thus, all severity levels seem to benefit from SMART compared to treatment options with SABA. The high benefit of SMART in patients with severe asthma might also, in our population, be associated with the suppression of underlying bronchial inflammation representing a key mechanism in disease pathogenesis [11]. Results from the recently published SHAMAL study showed that even a reduction in ICS is possible in controlled patients on benralizumab [15]. The positive effect of as-needed ICS is even indicated by the tendency toward a lower need for systemic steroids in SMART-treated patients. Nevertheless, the individual choice of therapy cannot be evaluated in all the patients, as there might be biases. Over the last 2 years, the proportion of combined therapy increased, indicating the awareness of treating physicians.

The strengths of our study are based upon its large sample size and its careful patient selection due to GAN inclusion criteria. Limitations include a cross-sectional, observational design, thus reporting only

associations and no causal relationship. Additionally, in up to 40% of the total patients, the type of reliever therapy was not reported. We show here that in patients with severe asthma, the GINA update from 2019 led to increasing numbers of patients using anti-inflammatory reliever therapy instead of SABA. To our knowledge, this is the first study that evaluates the changes of therapy after GINA guideline update in 2019 with the evidence of clinical improvement in association with SMART therapy in patients with severe asthma and under biologic therapy. By translating these data into clinical daily routine, we highlight the essential need to implement the GINA guideline changes to contribute to a better clinical outcome in patients with severe asthma.

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