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Maintenance OCS Were Used More Frequently Than Biologics in Patients with Uncontrolled GINA 4/5 Asthma in Germany in 2019

Katrin Milger[1], Dirk Koschel[2], Dirk Skowasch[3], Hartmut Timmermann[4], Olaf Schmidt[5], Karl-Christian Bergmann[6], Claus Neurohr[7], Robert Lindner[8], Sebastian Heck[9], Johann Christian Virchow[10]

[1]Division of Pulmonology, Department of Internal Medicine, Medical University of Graz, Graz, Austria; [2]Division of Pneumonology, Medical Department I, University Hospital Carl Gustav Carus, Dresden and Fachkrankenhaus Coswig, Lung Centre, Coswig, Germany; [3]Department of Internal Medicine II – Pneumology, University Hospital Bonn, Bonn, Germany; [4]Schwerpunktpraxis Colonnaden, Hamburg, Germany; [5]Pneumologische Gemeinschaftspraxis und Studienzentrum KPPK, Koblenz, Germany; [6]Institute for Allergology, Charité – Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Berlin, Germany; [7]Abteilung für Pneumologie und Beatmungsmedizin, Robert-Bosch-Krankenhaus Lungenzentrum, Stuttgart, Germany; [8]IQVIA Commercial GmbH & Co. OHG, Frankfurt Am Main, Germany; [9]GlaxoSmithKline GmbH & Co. KG, Munich, Germany; [10]Abteilung Pneumologie & Interdisziplinäre Internistische Intensivmedizin, Universitätsmedizin Rostock - Zentrum für Innere Medizin, Medizinische Klinik I, Rostock, Germany

Correspondence: Katrin Milger, Division of Pulmonology, Department of Internal Medicine, Medical University of Graz, Auenbruggerplatz 15, Graz, 8036, Austria, Email katrin.milger-kneidinger@medunigraz.at

Purpose: Asthma is affecting 4–5% of all adults (10% of children) in Germany, ≥ half are inadequately controlled. In 2019 up to 54 thousand patients suffered from severe uncontrolled asthma, 52% were treated/co-treated by pneumonologists. 45% of them had continuous oral corticosteroid (OCS)- and short-acting β2-agonist (SABA) overuse for ≥2 years. The aim of the current study was to analyze the main treatments, escalation schemes and the adherence to the GINA recommendations.

Patients and Methods: Retrospective analysis in 2021 based on data from January to December 2019 in Germany, using the IQVIA™ LRx prescription database and the IQVIA™ Disease Analyzer database containing anonymized electronic medical records as the main data sources.

Results: In 2019 25,200 patients with severe, uncontrolled asthma treated in a pneumonologist´s practice in Germany received GINA 3 (0,4%), GINA 4 (76%) or GINA 5 therapy (24%) during the study year compared to 59% GINA 5 therapy in the 5–10% (1,500–3,000) co-treated in a specialized outpatient department. In Pneumonologists` practices the most frequent choice in GINA 5 was OCS in 69% of patients (biologicals 37%, long-acting muscarinic antagonist (LAMA) 20%) compared to 66% biologicals, 55% OCS, and 25% LAMA in the outpatient department. 54,958 of 613,000 GINA 4/5 patients were treated with OCS, 9,725 even with doses above the so called "Cushing threshold" for prednisolone of 2700 mg/year. After introduction of a biological treatment, patients reduced their SABA prescriptions by 28%, OCS by 55%, and OCS overall exposure by 40%, one-third did not need OCS anymore.

Conclusion: In 75% of patients with uncontrolled asthma for ≥2 years therapy was not escalated beyond GINA 4 or low dose OCS was used as the most frequent add-on treatment in GINA 5 contradictory to treatment recommendations. Use of biologics reduced on demand rescue medication and OCS use.

Keywords: prescription database, disease analyzer, uncontrolled asthma, biological treatment, OCS use, Germany, guideline adherence

Introduction

Severe asthma has been recognized as a major unmet need.[1] It is also important in terms of health economics, as this minority of patients accounts for the majority of medical resource use.[2] Over the years asthma treatment recommendations have changed and are currently based on the level of asthma control.[3,4]

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A recently published epidemiological retrospective observational study provided data that in 2019 54,000 patients in Germany treated according to NVL/GINA step 4/5 had evidence suggestive for poor asthma control. About 52% of these severe uncontrolled patients with asthma were treated/co-treated by pneumonologists and were seen regularly at a frequency of approximately once per quarter.[5] About 45% of them had continuous oral corticosteroid (OCS)- and short-acting β2-agonist (SABA) overuse for ≥2 years (26% for ≥3 years, and 16% for ≥4 years).[5]

Thus, the aim of the current study was to analyze the main treatments and the escalation schemes in the management of these uncontrolled asthma patients in Germany in 2019 and to assess the adherence to the GINA recommendations.

Material and Methods

Study Design and Materials

The study design and methods have been published previously.[5,6] Briefly, the analyses were performed retrospectively based on data from January to December 2019 in Germany, and were supported by an Expert committee of pneumologists from different hospitals and expert practices who defined the patient cohorts, the methodology and the data analyses in cooperation with GlaxoSmithKline.

Data Sources

To analyze the main treatments and the escalation scheme in the management of severe uncontrolled asthma in Germany in 2019 the IQVIA™ Longitudinal Prescription Data (LRx) was used as main data source for patient quantification. This longitudinal anonymized prescription database contains approximately 80% of the statutory health insurance (SHI/GKV (Gesetzliche Krankenversicherung)), under which ~90% of the German population are insured, prescriptions claimed in retail pharmacies. IQVIA™ LRx contains most relevant information from SHI prescriptions such as prescribed product, substance and pack (identified via Pharmazentralnummer PZN) as well as prescription date and prescriber specialty. In addition, basic patient demographics such as age and gender are included as well as the location of the prescriber on KV (Kassenärztliche Vereinigung, Association of Statutory Health Insurance Physicians, 17 regional KVs in Germany) - district level (63 districts in Germany). The main data source for diagnosis was the IQVIA™ Disease Analyzer.[7] This database contains anonymized electronic medical records from a representative sample of office-based general practitioners (GPs), pneumonologists and pediatricians in Germany.[7] Diagnosis according to ICD 10, medical histories in one practice, lab tests and other detailed information is available, and updated monthly.

Selection of Patients with Uncontrolled NVL 4/5 Asthma

The selection criteria for the cohort of patients with severe or difficult-to-treat asthma were first: maintenance therapy for at least half of the study period as a quality criterion to the data, in order to select patients with good database observability and not only seasonal flares of high-dose medication, and second: treatment primarily according to GINA[3] step 4 or 5 (Table 1) or treatment according to GINA step 3 and noticeable step up treatment during the study period for at least 120 days OCS+ICS+LABA+ (LAMA or leukotriene-receptor antagonists (LTRA)) as criteria to select patients with difficult to treat asthma.

In the subset of patients with GINA 4/5 asthma patients who had high amounts of OCS prescriptions, high amounts of SABA prescriptions or both, were selected as uncontrolled. Several cutoffs were discussed and finally, the following intermediate scenario was selected: Patients that had a score of ≥2 were flagged as high OCS (prescriptions from pneumonologists scored 1.0, prescriptions from other specialists or GPs scored 0.75). SABA: Patients with at least 3 SABA prescriptions during 2019 issued on days with no prescription of ICS-containing maintenance medication were flagged as high SABA.

Human Ethics Statement

The database used includes only anonymized data in compliance with the regulations of the applicable data protection laws. German law allows the use of anonymous electronic medical records for research purposes under certain

Table 1 GINA Step Assignment (Adapted from GINA 2019)

Step	Definition
1	• No maintenance therapy
2	• Low dose ICS only • Oral controller** only
3	• Low dose ICS + LABA and/or oral controller • Medium dose ICS only
4	• Medium dose ICS/LABA • Medium/high dose ICS + LABA and/or oral controller • Low dose ICS + LABA + LAMA
5	• Any high dose ICS + OCS* • Any ICS/LABA + OCS* • Any medium/high dose ICS/LABA + LAMA (Triple***) • Biologics

Notes: *OCS: Only prescriptions of low dose and high pack size were included to restrict to maintenance therapy, rather than acute high dose use. **: LTRA and theophylline (rarely used). ***: At the time of the study, no fixed triple treatments were approved for asthma in Germany. Classification makes no distinction between free or fixed combination options whereby fixed ICS/LABA is more prevalent than free combinations. Children's classification was done by the same rules as for adults. Differences are nuanced in step 4 and could not be resolved in RWD. Differences mainly arise from different ICS dosage thresholds translating into low/medium/high daily dose. High dose ICS/LABA in the absence of add-on (Biologic, OCS, LAMA) was not classified as GINA 5 as ICS daily dose is estimated from refill distances with some uncertainty. In the further steps of the study, GINA 4 and GINA 5 patients were analyzed as one group.
Abbreviations: ICS, inhaled corticosteroids; LABA, long-acting β2-agonist; LAMA, long-acting muscarinic antagonist; OCS, oral corticosteroid.

conditions. According to this legislation, it is not mandatory to obtain informed consent from patients or approval from a medical ethics committee for this type of observational study that contains no directly identifiable data.

Since patients were only queried as aggregates and no protected health information was available for queries, no Institutional Review Board approval was required for the use of this database or the completion of this study.

Results

Treatment of Patients with Severe Uncontrolled Asthma

In 2019 25,200 patients with severe uncontrolled asthma in Germany received at least one asthma-related prescription in a pneumonologist´s practice (Figure 1). The analysis of the highest treatment step showed that 0.4% were treated according to GINA 3, 76% according to GINA 4% and 24% according to GINA 5 during the study year (Figure 1). 5–10% (1,500–3,000) of the patients with severe, uncontrolled asthma treated by a pneumonologist in Germany were treated or co-treated by a pneumonologist in an outpatient department of a tertiary referral center during the study year 2019 (Figure 1). In 59% of these patients GINA 5 treatment was prescribed, compared to 24% treated exclusively in pneumonologists´ practices (Figure 1).

Most Frequent Choice in GINA 5 Therapy in Germany in 2019

In patients with severe, uncontrolled asthma and ≥1 prescription by a pneumonologist the most frequent treatment choice when escalating to GINA 5 treatment was the use of low dose OCS in 69% of patients (35% < 120 days per year, 34% ≥120 days per year) (Figure 2). About 50% of the patients received one prescription of an OCS < 10 mg in maximum size (N3 pack, equivalent of 100 tablets), others repeated low dose OCS. The second most common treatment choice was

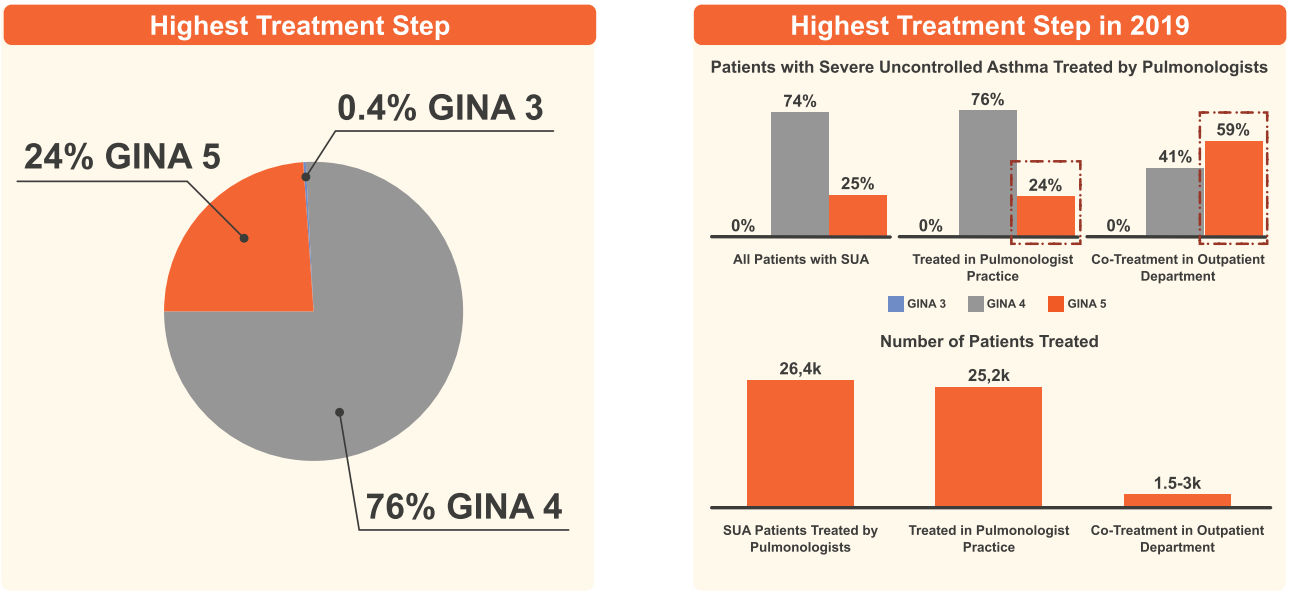

Figure 1 Treatment of patients with severe, uncontrolled asthma in Germany in 2019. 75% of patients with severe, uncontrolled asthma treated in pneumonologist practices were not escalated on GINA 5 therapy.
Notes: mod. acc. IQVIA™ LRx MAT 12/2019: Patients with severe, uncontrolled asthma and ≥1 prescription by a pneumonologist. GINA 5 treatment counted if prescribed ≤90 days after the last OCS prescription. Co-treatment means prescription in 2019 by pneumonologist in practice and in the outpatient department.
Abbreviations: SUA, severe, uncontrolled asthma; k, thousand.

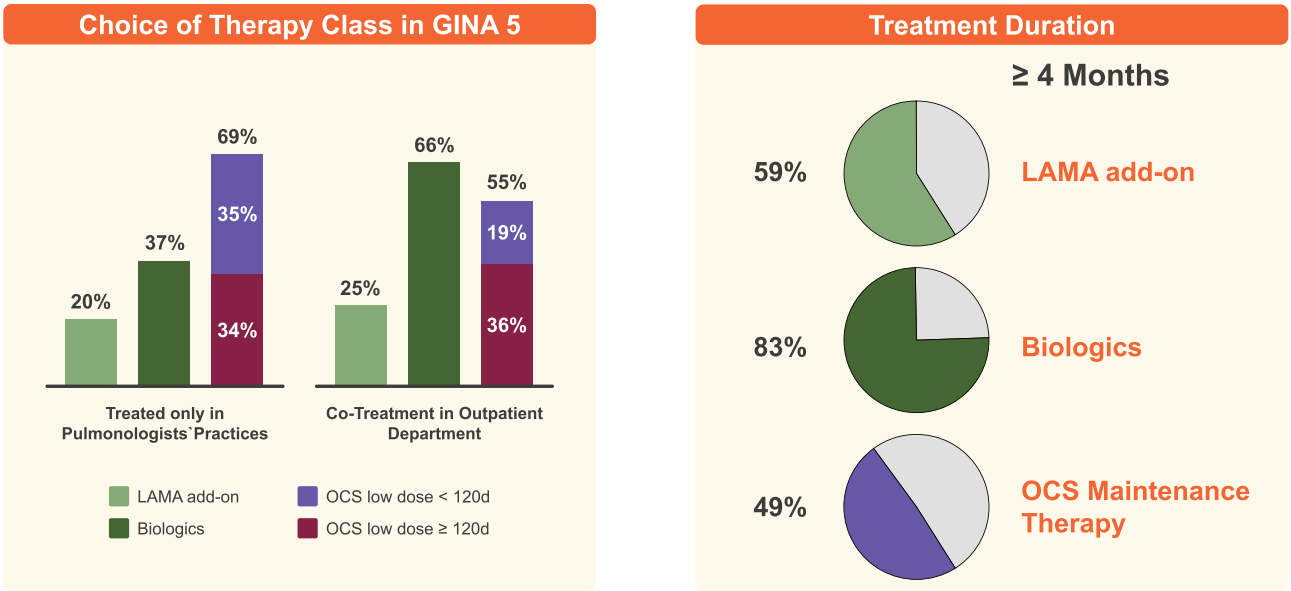

Figure 2 Overview about frequency of different treatments in GINA 5 patients in Germany in 2019. Low dose OCS was the most frequent GINA 5 treatment in Germany (69%) in patients treated in pulmonologists´ practices.
Notes: mod. acc. IQVIA™ LRx MAT 12/2019: Patients with severe asthma and ≥1 prescription by a pulmonologist.
Abbreviations: LAMA, long-acting muscarinic antagonist; OCS, oral corticosteroid.

adding a biologic medication (37%) and in 20% a long-acting muscarinic antagonist was chosen as add-on therapy (Figure 2).

If a patient was co-treated by a tertiary referral outpatient department, the most frequent choice was a biological medication in 66% of all cases, followed by low dose OCS in 55% (19% < 120 days and 36% ≥120 days per year) and a LAMA add-on in 25% of the cases (Figure 2).

A treatment duration of ≥4 months was observed in 49% of all patients that received an OCS maintenance therapy compared to 59% of patients with LAMA add-on treatment and 83% of all patients with biological therapy (Figure 2).

OCS Use in Patients with GINA 4/5 Asthma in Germany in 2019 (Excluding Biologic Users)

We classified 625,000 asthma patients as receiving treatment, according to GINA 4 or 5 in Germany in 2019. After the exclusion of 12,000 patients receiving biological treatment 54,958 patients of the 613,000 patients with GINA 4/5 treatment received OCS of >500 mg/year in 2019. About 37,296 patients reached or exceeded this threshold because of an acute treatment with OCS, 19,947 because of maintenance OCS therapy; some patients reached the threshold for both categories (Figure 3). About 9,725 patients (5,296 in category "acute OCS treatment", 2,903 in category "maintenance OCS treatment") exceeded the yearly "Cushing threshold" of 2700 mg prednisolone (Figure 3).

Biological Treatment in GINA 5 Patients

Patients with severe asthma who were escalated to GINA 5 therapy were analyzed if data of at least 1 year before and after the start of GINA 5 treatment was available as well as at least 180 days on GINA 5 therapy. In the year after introduction of a biological treatment patients did reduce their SABA prescriptions by 28% compared to the year before and their high dose OCS prescriptions by 55%, although this group of patients had more exacerbations in their history than patient groups treated with other GINA 5 medications (Figure 4). In this real-life setting, one-third of patients treated with OCS were completely tapered off; the overall OCS exposure (mg) was reduced by 40% (Figure 4) in the year after the introduction of a biological treatment. LAMA add-on therapy was used more frequently in patients with fewer exacerbations in the past. In the year after the introduction of the LAMA treatment, there was a small reduction in the number of patients with OCS prescriptions from 33% to 27%, with no change in the mg OCS exposure and a small increase in the number of SABA prescriptions (+2%) or high dose OCS prescriptions (+4%) (Figure 4).

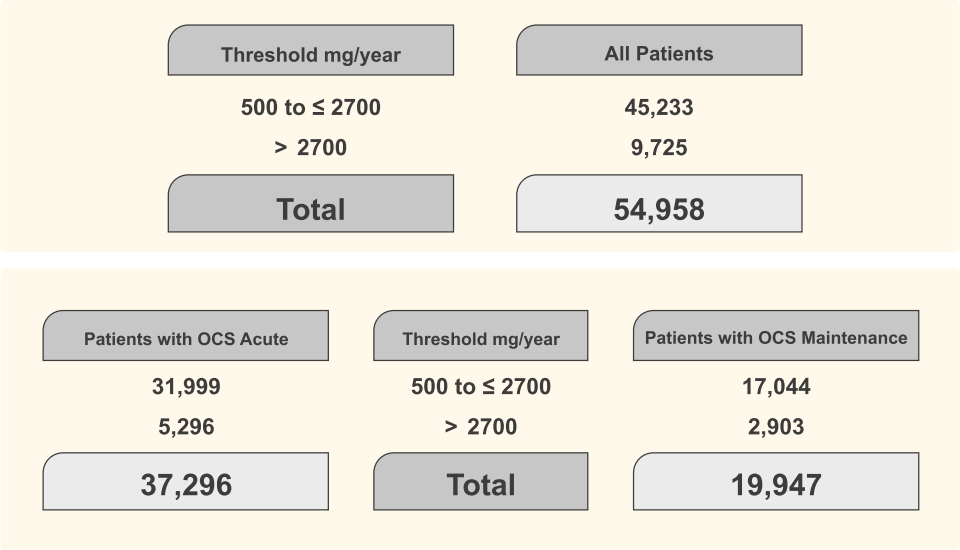

Figure 3 OCS Use in Patients with GINA 4/5* Asthma in Germany in 2019. 55,000 patients of 613,000 patients with GINA 4/5 treatment received OCS of > 500 mg/year in 2019; 37,296 because of acute and/or 19,947 because of maintenance therapy. 9,725 patients were above the yearly threshold of 2700 mg prednisolone considered relevant for iatrogenic Cushing's syndrome.

Notes: mod. acc. IQVIA™ LRx MAT 12/2019: *625,000 patients treated according to GINA 4 or 5; 12,000 patients receiving biological treatment were excluded from this analysis.

Abbreviations: OCS, oral corticosteroid.

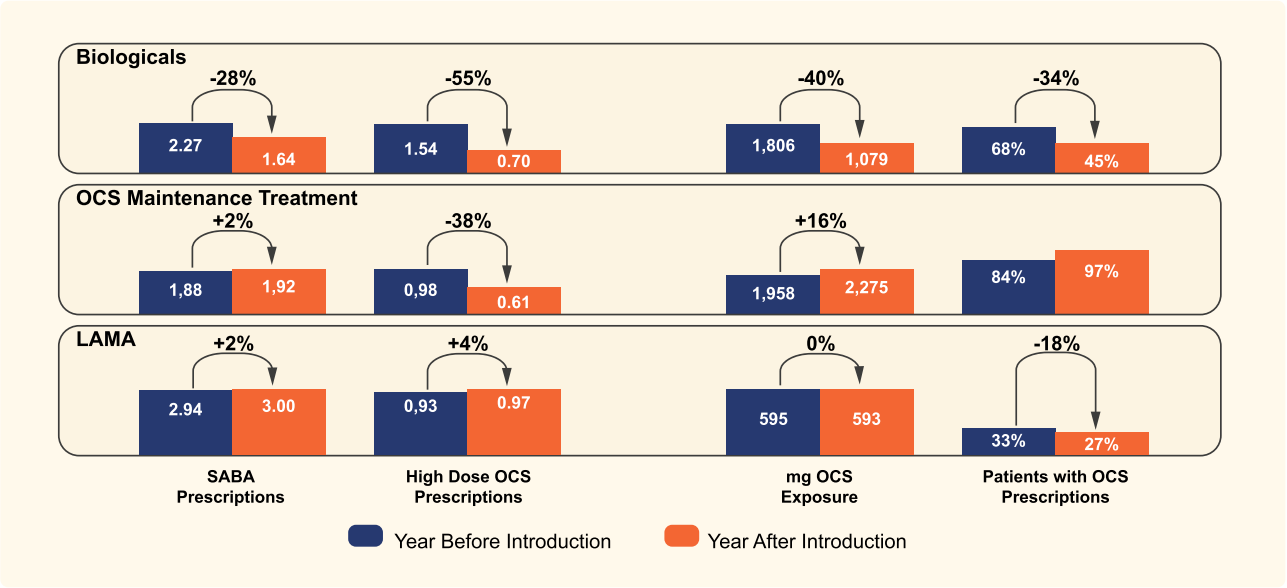

Figure 4 Effect of biological treatments on OCS and SABA prescriptions in the year after introduction as add-on GINA 5 therapy in patients with severe asthma. Reduction of high dose OCS prescriptions by 55% and SABA prescriptions by 28%.

Notes: mod. acc. IQVIA™ LRx MAT 12/2019: Patients with severe asthma escalated to GINA 5 therapy with data of at least 1 year before and after the start of GINA 5 treatment and at least 180 days on GINA 5 therapy. Biological and OCS treatment could overlap, and in patients receiving LAMA we analyzed only patients receiving LAMA as the only add-on GINA 5 treatment (combination step up with biologics or maintenance OCS was excluded).

Abbreviations: LAMA, long-acting muscarinic antagonist; OCS, oral corticosteroid; SABA, short-acting β2-agonist.

Discussion

The present study aimed to analyze the main treatments and treatment algorithms in the management of severe uncontrolled asthma in Germany in 2019 as well as the adherence to the GINA recommendations.

Current asthma recommendations are based on the level of asthma control.[3,4] A recent publication indicated that 54 thousand patients in Germany with GINA 4/5 asthma were uncontrolled in 2019.[6] About 52% of these patients with uncontrolled asthma were treated/co-treated by pneumonologists and were seen regularly approximately once per quarter year.[5] About 5% of them were uncontrolled for ≥2 years.[5] Despite this situation, the full treatment options in asthma with escalation to GINA 5 were often not applied. As shown in our analysis, only 24% of patients with uncontrolled asthma treated in a pneumonologist´s practice were treated according to GINA 5 recommendation during the study year, and 75% were not escalated beyond GINA 4. About 22% of GINA 4 treated uncontrolled asthma patients received already high dose of ICS-LABA. In patients treated by a pneumonologist in a tertiary referral outpatient department, the probability to receive treatment according to GINA step 5 was more than doubled (59% of patients) compared to treatment in pneumonologists` practices (24% of patients). However, the number of uncontrolled GINA 4/5 asthma patients treated in an outpatient department was small, amounting to only 5–10% (1,500–3,000) of the patients. The underlying reasons for these findings remain unclear and cannot be answered from such a database analysis. Possible reasons that may have influenced management decisions of pneumonologists which could not be analyzed here include differentiation between severe and difficult-to-treat asthma and biomarker levels required for prescription of specific biologics. Finally, even though guidelines recommend to preferably use biologics, and not mOCS as step 5 treatment, licensing trials of biologics have included patients based on previous OCS use (either continuous or as defining exacerbations) and definitions of severe asthma also partially rely on previous OCS exposure. This might also be a reason why pneumonologist took a conservative approach, "collecting" prescriptions of OCS first for proof of severe asthma and fulfillment of licensing criteria, before moving to biologics. Still, patients had signs of uncontrolled asthma for 2 or more years, suggesting that a biologic might have been indicated earlier.

If a patient with severe, uncontrolled asthma was treated with GINA 5 medication in a pneumonologist´s practice the most frequent step 5 treatment was low dose OCS in 69% of patients. Thus, contradictory to current treatment recommendations, low dose OCS was used more frequently than biologics when escalating to GINA 5.[4,5] A biological treatment was used in 37% of the patients and a LAMA was added in only 20% of all cases. Again, there were different treatment preferences when

patients were managed in tertiary referral outpatient departments, where a biological medication was chosen in 66% of all cases, followed by low dose OCS 55% and a LAMA add-on in 25%.[5] Thus, the option of using one of the different biological treatments in severe asthma was used to a much higher extent in outpatient departments than in pneumonologists´ practices. If a patient received a biological treatment, it was used according to treatment recommendations as maintenance controller[4] in 83% of patients (≥4 months treatment duration). One of the reasons for a preferential prescription of biologics in outpatient departments vs pneumologists' practices could be the fact that patients with persistently uncontrolled asthma on OCS were more likely to be referred to specialized outpatient departments for evaluation of biologic therapy. Even though in Germany pneumonologists´ practices can initiate biologic treatments without consultation of a tertiary reference center, referrals are frequent with new and/or costly drugs.

In the group of patients treated according to GINA 4 or 5, excluding those that were treated with biologicals (n=613,000: 625,000 GINA 4/5 minus 12,000 treatment with biologicals) 54,958 patients received OCS in doses that have been linked to side effects (≥500 mg/year).[8] 37,296 patients received the OCS for an acute treatment and 19,947 for maintenance treatment. An OCS prescription might be due to other indications than asthma, and in some cases, pneumonologists are also forced to continue prescribing OCS because of comorbidities such as concomitant rheumatoid arthritis or steroid-induced adrenal insufficiency unrelated or only indirectly related to asthma therapy. These cases, however, were reduced to a small number by using Disease Analyzer database in addition to the prescription data. There was still a high number of patients receiving systemic corticosteroid doses, which are associated with an increased risk of severe side effects.[8] There is mounting evidence suggesting that even short courses of systemic corticosteroids increase the risk of adverse events including osteoporosis, hypertension and gastrointestinal ulcers/bleeds in addition to serious impacts on mental health.[8–16] Of significant importance, cumulative doses of systemic corticosteroids (SCS) were associated with a clear dose-dependent increase in the risk of developing an adverse event.[17] The dose–response relationship for cumulative SCS exposure with most adverse outcomes appears to begin at cumulative exposures of 1 g to < 2.5 g and for some outcomes at cumulative exposures of only 0.5 g to < 1g.[17] Furthermore, 8,199 patients of our data set were treated with doses above the "Cushing threshold" for prednisolone of 2700 mg/year. While SCS-related weight gain may further impact negatively on asthma control,[1] the many systemic effects associated with long-term SCS use are well studied and described,[8,17,18] highlighting the need for steroid-sparing therapies in the treatment of asthma in Germany and supporting similar results from others.[19]

Within the first year after the introduction of a biological patients were able to reduce their SABA prescriptions by 28% compared to the year before and their high dose OCS prescriptions by 55%. The overall OCS exposure (mg) was tapered by 40%, and one-third of the patients treated with OCS were able to completely discontinue them. Thus, our analysis confirms the results of controlled studies[20,21] that biological therapies are useful for reducing OCS use and maintaining asthma control. In summary, 52% of the 54,000 uncontrolled GINA 4/5 asthma patients were treated by a pneumonologist in Germany. Although uncontrolled for several years, in 75% of patients treatment was not escalated to GINA 5 and the most frequent add-on treatment was low dose OCS.

A potential limitation of the study is its retrospective design. As with all retrospective analysis, there is a potential risk of bias and the dynamic changes in therapies available and updates to guidelines can change the relationships over time. Further, we cannot provide any data on whether the prescribed medications had actually been taken. Furthermore, specialized outpatient departments are mainly treating a selective group of patients where OCS discontinuation might not be possible anymore. On the other hand, the data pool used is very extensive, containing approximately 80% of the statutory health insurance prescriptions claimed in retail pharmacies in Germany, and should outrank this possible risk. In addition, the representation of real-life practices in Germany over at least one year is a valuable source.

Conclusion

In 75% of patients with uncontrolled severe asthma for ≥2 years therapy was not escalated beyond GINA 4 and low dose OCS were the most frequently used option in GINA 5 treatment despite management by pneumonologists. The introduction of biologicals reduced the need for rescue medication as well as for maintenance OCS.

Abbreviations

GKV, gesetzliche Krankenversicherung; GP, general practitioner; ICS, inhaled corticosteroid; KV, kassenärztliche Vereinigung; LABA, long-acting β2-agonist; LAMA, long-acting muscarinic antagonist; OCS, oral corticosteroid; PZN, Pharmazentralnummer; RP, respiratory physician; Rx, prescription; SABA, short-acting β2-agonist; SCS, systemic corticosteroid; SHI, statutory health insurance.

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Disclosure

KCB and OS have no relevant competing interests to disclose for this work. SH is a GSK employee and shareholder. KM reports speaker and/ or advisory fees from AstraZeneca, Chiesi, GSK, Novartis, Sanofi. CN received honoraria and advisory board fees from GSK, Sanofi, AstraZeneca and Novartis. DS received honoraria for lectures and/or consultancy from AstraZeneca, Bayer, Berlin-Chemie, Boehringer, Sanofi, Chiesi, GSK, Janssen, Novartis, Pfizer. RL is an employee of IQVIA. IQVIA is a technology service provider that carried out the database studies within the scope of a commercial engagement with GSK. DK reports personal fees from GSK, AstraZeneca, Sanofi Aventis, and Novartis. JCV has lectured for and received honoraria from AstraZeneca, Avontec, Bayer, Bencard, Bionorica, Boehringer-Ingelheim, Chiesi, Essex/ Schering-Plough, GSK, Janssen-Cilag, Leti, MEDA, Merck, MSD, Mundipharma, Novartis, Nycomed/Altana, Pfizer, Revotar, Sandoz-Hexal, Stallergens, TEVA, UCB/ Schwarz-Pharma, Zydus/Cadila and has participated in advisory boards for Avontec, ALK, Boehringer-Ingelheim, Chiesi, Essex/Schering-Plough, GSK, Janssen-Cilag, LETI, MEDA, MSD, Mundipharma, Novartis, Regeneron, Revotar, Roche, Sanofi-Aventis, Sandoz-Hexal, TEVA, UCB/Schwarz-Pharma and has received research grants from Deutsche Forschungsgesellschaft, Land Mecklenburg-Vorpommern, GSK, MSD and is a full-time employee of the Universitätsmedizin Rostock. The authors report no other conflicts of interest in this work.

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