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Таргетная терапия тяжёлой бронхиальной астмы: смена биологического препарата в реальной клинической практике — причины и следствие

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АННОТАЦИЯ

Обоснование. Сложность выбора генно-инженерного биологического препарата для лечения тяжёлой бронхиальной астмы обусловлена перекрёстами эндотипов и фенотипов заболевания. Ошибки выбора генно-инженерного биологического препарата приводят к отмене и/или смене препарата вследствие недостаточной эффективности терапии.

Цель — определить причины прекращения таргетной терапии и эффективность смены биологического препарата у больных тяжёлой бронхиальной астмой в реальной клинической практике.

Материалы и методы. Участниками исследования были пациенты с тяжёлой бронхиальной астмой (*n*=116) из регистра Свердловской области. Пациенты были разделены на 3 группы: «Продолжающие» (группа 1), «Стопперы» (группа 2) и «Переключённые» (группа 3), в которых определяли предикторы отмены и смены генно-инженерного биологического препарата, причины отмены стартового генно-инженерного биологического препарата, схемы переключения, эффективность терапии после переключения (по объёму форсированного выдоха за первую секунду, потребности в системных глюкокортикоидах, достижению стойкого контроля над бронхиальной астмой, динамике тестов ACT, AQLQ, SNOT-22).

Результаты. Из 116 пациентов регистра в 17,2% случаев произошла отмена, в 12,1% — смена препарата. «Стопперы» реже страдали хроническим риносинуситом с полипами носа, имели более ранний дебют бронхиальной астмы. В группе «Переключённых» был выше уровень эозинофилов крови. В 45% случаев терапия была отменена по личным причинам пациентов. Основная причина переключения (92,8%) — неэффективность терапии по тяжёлой бронхиальной астме и/или хроническому риносинуситу с полипами носа. Чаще переключали с омализумаба и бенрализумаба. Препаратом выбора при переключении был дупилумаб. Через 12 месяцев после переключения отмечалось улучшение показателей объёма форсированного выдоха за первую секунду (на 21,2%); тестов ACT (на 86,4%), AQLQ (на 52,5%), SNOT-22 (на 48%); потребность в системных глюкокортикоидах снизилась до нуля. Стойкого контроля без и с учётом объёма форсированного выдоха за первую секунду достигли 62,5 и 50% пациентов соответственно.

Заключение. Тщательный отбор пациентов на таргетную терапию позволяет минимизировать неудачи стартового препарата до 12,1%. Смена стартового генно-инженерного биологического препарата, направленного на блокирование только эозинофилов или только IgE, вследствие его неэффективности на препарат с двойным механизмом действия существенно улучшает результаты объёма форсированного выдоха за первую секунду, тестов ACT, AQLQ и SNOT-22, а также снижает потребность в системных глюкокортикоидах.

Ключевые слова: тяжёлая бронхиальная астма; таргетная терапия; генно-инженерные биологические препараты переключения.

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Targeted Therapy for Severe Asthma: Switching Biological agents in Real Clinical Practice — Causes and Consequences

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ABSTRACT

BACKGROUND: The complexity of choosing a genetically engineered biological drug for the treatment of severe bronchial asthma is due to the intersection of disease endotypes and phenotypes. Mistakes in biological choice lead to the discontinuation and/or switching of the drug because of insufficient effectiveness of therapy.

AIM: To determine the reasons for stopping targeted therapy and biological switching effectiveness in patients with severe bronchial asthma in clinical practice.

MATERIALS AND METHODS: Patients with severe bronchial asthma (*n*=116) from the Sverdlovsk region register were divided into three groups: (1) continuous, (2) stoppers, and (3) switchers. Predictors of biological withdrawal and switching, reasons for the first biological stopping, switching schemes, therapy effectiveness after switching according to the asthma control test (ACT), asthma quality of life questionnaire (AQLQ), 22-item sinonasal outcome test [SNOT-22], forced expiratory volume in the first second, need for systemic glucocorticosteroids, and achievement of strong asthma control were determined.

RESULTS: Of the 116 patients in the registry, 17.2% were stoppers and 12.1% were switchers. Stoppers suffered from chronic rhinosinusitis with nasal polyps less often and had an earlier asthma onset. Switchers had higher blood eosinophil levels. Therapy was canceled for personal reasons in 45% of the patients. The ineffectiveness of therapy in severe bronchial asthma and/or chronic rhinosinusitis with nasal polyps was the main reason for switching (92.8%) from omalizumab and benralizumab. The drug of choice for switching was dupilumab. Indicators improved, namely, ACT by 86.4%, AQLQ by 52.5%, SNOT-22 by 48%, and forced expiratory volume in the first second by 21.2%), and the need for systemic glucocorticosteroids decreased to 0 in 12 months after switching. Strong control was achieved in 62.5% of the patients when excluding the forced expiratory volume in the first second, and 50% of patients when including the forced expiratory volume in the first second.

CONCLUSION: Careful selection of targeted therapy patients minimizes the failures of the starting drug to 12.1%. Switching the starting genetically engineered biological drug, aimed only at blocking eosinophils or only at blocking IgE, because of its inefficiency, to a drug with a dual mechanism of action leads to a significant improvement in ACT, AQLQ, SNOT-22, forced expiratory volume in the first second, and absence of systemic glucocorticosteroids.

Keywords: severe bronchial asthma; targeted therapy; genetically engineered biological drug switching.

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List of abbreviations

ACT — Asthma Control Test
AD — atopic dermatitis
AE — adverse event
AQLQ — Asthma Quality of Life Questionnaire
AR — allergic rhinitis
BA — bronchial asthma
BMI — body mass index
CRS — chronic rhinosinusitis
CRSsNP — chronic rhinosinusitis without nasal polyps
CRSwNP — chronic rhinosinusitis with nasal polyps
FeNO — nitric oxide fraction in exhaled air
FEV_1 — forced expiratory volume in the first second
GEBD — genetically engineered biological drug
IL — interleukin
NSAIDs — nonsteroidal anti—inflammatory drugs
SA — severe asthma
SGCS — systemic glucocorticosteroids
SNOT-22 — Sino—Nasal Outcome Test
VAS — visual analog scale

BACKGROUND

In recent decades, detailed studies of bronchial asthma pathogenesis have permitted the development of genetically engineered biologic drugs (GEBDs) for the treatment of severe bronchial asthma (SA). The mechanism of action of targeted drugs currently available in routine practice (omalizumab, mepolizumab, reslizumab, benralizumab, and dupilumab) is aimed at different regions of T2 inflammation [1]. Thus, omalizumab acts on IgE immunoglobulin, mepolizumab, and reslizumab target interleukin (IL)-5, benralizumab binds to the alpha subunit of the IL-5 receptor, and dupilumab inhibits the IL-4 and IL-13 pathways by binding with the alpha subunit of the IL-4 receptor [2–4]. Because direct comparisons between these biologics are rare, the superiority of one biologic over the other could not be asserted [2, 5–7]. Selecting an optimal drug can be challenging because of the heterogeneity of the pathogenetic mechanisms of T2 inflammation [5, 6, 8]. Some authors report that up to a third of patients with SA have overlapping criteria for the prescription of four biologics, and 75% of the patients meet the requirements for two or more biologics [9]. In turn, an error in selecting a target for therapy and consequentially, the starting monoclonal antibody, frequently results in the discontinuing and/or switching of the targeted drug because of a suboptimal clinical response [5, 6, 8].

The **study aimed** to determine the reasons for the discontinuation of targeted therapy and biologic switching effectiveness in patients with SA in real clinical practice.

MATERIALS AND METHODS

Research design

Adult patients (≥18 years old) with SA from the territorial registry of the Sverdlovsk region receiving targeted therapy participated in the observation cohort retrospective study.

Inclusion/exclusion criteria

When patients were included in the registry for targeted therapy, the diagnosis of SA was verified by specialists based on the American Thoracic Society and the European Respiratory Society criteria [10, 11]. Next, a GEBD was prescribed according to the disease phenotype. Patients with an allergic SA phenotype (J45.0) received first-line omalizumab. In case the body weight and/or total IgE level of the patient did not allow the calculation of the omalizumab dose and the SA was combined with atopic dermatitis (AD), then dupilumab was prescribed. The allergic phenotype was determined by combining a positive allergy history with positive allergy tests (skin tests and/or specific IgE and/or Phadiatop test). Patients with nonallergic eosinophilic asthma (J45.1) were treated using anti–IL5 or anti–IL4R, 13 drugs. A nonallergic eosinophilic phenotype was established with a negative allergy history, negative allergy tests, and a peripheral blood eosinophil level of ≥150 cells/mcL [11,12]. Furthermore, this phenotype was characterized by the presence of chronic rhinosinusitis with/without nasal polyps (CRSwNP/CRSsNP) and an intolerance to nonsteroidal anti-inflammatory drugs (NSAIDs). The choice of drug for patients with nonallergic eosinophilic asthma was determined by their peripheral blood eosinophils levels. Mepolizumab and dupilumab were administered in patients with an eosinophil count of ≥150 cells/μL and <1,500 cells/μL, respectively. Benralizumab or reslizumab was preferred at blood eosinophil levels of ≥400 cells/μL. The mixed phenotype of SA (J45.8) suggested a combination of allergic and nonallergic components and the possibility of prescribing any class of GEBD, considering the clinical and laboratory characteristics of patients. As of April 2023, 157 cases of targeted therapy initiation were recorded in the registry. Of these cases, 15 were cases of therapy initiation with the second and third drugs in the same patient (13 patients with the second drug and 1 patient with the second and third drugs). The exclusion criteria for the patients were as follows: starting therapy before June 2019 (when the second GEBD became available for prescription in

the Sverdlovsk region), refusal to undergo therapy before the first injection (as per the patients' requests), and initiation of therapy after October 2022 (for patients to pass control visit month 4) (Fig. 1).

Study conditions

The patients were divided into group 1, patients continuing treatment; group 2, patients completing treatment (stoppers); and group 3, patients switching between biologics (switchers).

Study duration

The study was conducted from June 2019 to October 2022.

Description of the medical intervention

Biologics were selected based on the asthma phenotype, determined by the specialists' council, and their instructions. When monitoring patients during targeted therapy, indicators of their clinical condition, laboratory and instrumental examinations, use of healthcare resources, quality of life, number of injections, adverse events (AEs), reasons for therapy discontinuation, and drug switching were recorded.

Primary endpoint

The primary endpoint was to identify signs that were characteristic of stoppers and switchers.

Secondary endpoints

The secondary endpoints included the main reasons for the discontinuation of the first biologic, switching regimens, and therapy effectiveness after switching.

All causes for discontinuing and switching biologics were divided into the following eight categories:

- personal reasons (unwillingness or fear of new drugs, family circumstances, unmotivated reasons, and inability to combine treatment with a work schedule);
- achievement of SA control, which was regarded by the patient as a sign of the sufficiency of targeted therapy and a reason for refusing to continue it (the patients made the decision to stop therapy);
- AEs;
- ineffectiveness against SA;
- ineffectiveness against concomitant T2 pathology (chronic rhinosinusitis and AD);
- ineffectiveness against SA and concomitant T2 pathology;
- organizational reasons (delay in the purchase of drugs by hospitals, difficulties in organizing, examinations before each injection, and frequency of injections two times a month for dupilumab), and
- death.

Subgroup analysis

Not performed.

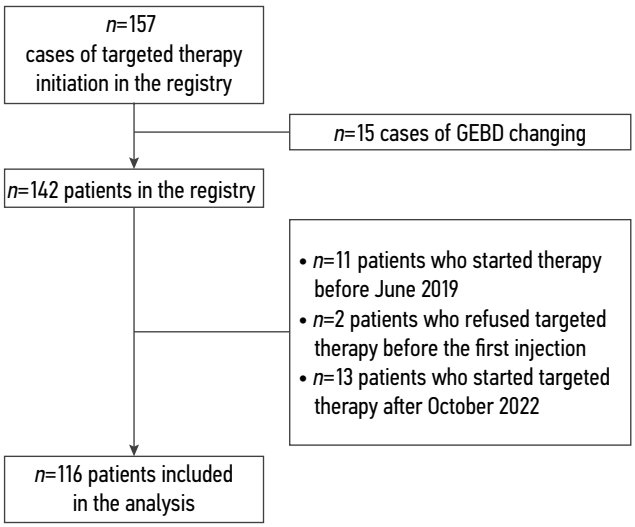

Fig. 1. Patients' enrollment scheme.
Note. GEBD, genetically engineered biologic drug.

Methods of outcome registration

Switching effectiveness was evaluated via the dynamics of separate indicators (asthma control test [ACT], forced expiratory volume in 1 second (FEV_1), asthma quality of life questionnaire [AQLQ], need for systemic glucocorticosteroids [SGCS], and sino-nasal outcome test [SNOT-22]) using the analysis of related populations (before–after) at the 4^{th} and 12^{th} months of therapy and a complex indicator, i.e., achievement of SA strong control. The absence of asthma exacerbations, nonrequirement of SGCS, ACT ⩾20 points and FEV_1 ⩾80% by the 12^{th} month of therapy would be considered a strong control of SA.

Ethical examination

The Local Ethics Committee of the Ural State Medical University of the Russian Ministry of Health reviewed this study. Patients signed a voluntary informed consent form to participate in the study.

Statistical analysis

Statistical analysis was performed using StatTech v. 3.1.7 (StatTech LLC, Russia). Quantitative variables were assessed for normality using either the Shapiro–Wilk test (<50 participants) or the Kolmogorov–Smirnov criterion (>50 participants).

Quantitative variables following a normal distribution were described using means (M) and standard deviations (SD), and the 95% confidence interval (95% CI) for the means was estimated. Quantitative variables following non-normal distribution were described using medians (Me) and lower and upper quartiles (Q_1–Q_3). Categorical data were described with absolute and relative frequencies. One-way analysis of variance and Tukey test, as a post hoc method (assuming equal variances), were performed when comparing three or more groups associated with a quantitative variable followed a normal distribution. The Kruskal–Wallis test and Dunn's

Table 1. Characteristics of patients with severe bronchial asthma taking into the study

Indicator	Total *n*=116	Group 1 Continuers *n*=82	Group 2 Stoppers *n*=20	Group 3 Switchers *n*=14	*p*
Women, *n* (%)	98 (84.5)	71 (86.6)	15 (75.0)	12 (85.7)	0.435
Men, *n* (%)	18 (15.5)	11 (13.4)	5 (25.0)	2 (14.3)	
Average age (years), M±SD (95% CI)	51.12±12.19 (48.88–53.36)	51.67±12.31 (48.97–54.37)	46.90±13.42 (40.62–53.18)	53.93±8.33 (49.12–58.74)	0.192
Average age at asthma onset (years), Me (Q_1–Q_3)	30.00 (12.50–41.00)	31.50 (18.25–40.75)	16.00 (7.50–29.00)	43.50 (23.50–50.75)	0.027* $p_{Switchers–Stoppers}$=0.032
BMI, kg/m^2, M±SD (95% CI)	28.44±6.23 (27.24–29.63)	28.74±6.53 (27.30–30.19)	27.39±5.87 (23.66–31.12)	27.56±4.75 (24.82–30.30)	0.671
Allergic rhinitis, *n* (%)	55 (47.4)	40 (48.8)	9 (45.0)	6 (42.9)	0.894
CRSwNP, *n* (%)	55 (47.4)	42 (51.2)	4 (20.0)	9 (64.3)	0.017* $p_{Continuers–Stoppers}$=0.027 $p_{Stoppers–Switchers}$=0.027
CRSsNP, *n* (%)	15 (12.9)	8 (9.8)	4 (20.0)	3 (21.4)	0.284
AD, *n* (%)	15 (12.9)	13 (15.9)	1 (5.3)	1 (7.1)	0.365
Hypersensitivity to NSAIDs, *n* (%)	38 (33.6)	24 (29.3)	8 (47.1)	6 (42.9)	0.272
Smoking, *n* (%)	14 (12.2)	9 (11.0)	3 (15.8)	2 (14.3)	0.818
Total IgE, IU/mL, Me (Q_1–Q_3)	168.30 (74.95–450.75)	189.00 (73.30–473.50)	207.00 (44.90–391.00)	133.00 (119.00–218.73)	0.891
Phadiatop, PAU/l, Me (Q_1–Q_3)	1.04 (0.08–7.21)	1.31 (0.08–7.86)	1.33 (0.10–6.29)	0.50 (0.03–4.32)	0.715
Peripheral blood eosinophils, cells/μL, Me (Q_1–Q_3)	489.00 (299.50–874.00)	466.50 (284.50–755.75)	390.50 (239.50–536.00)	881.50 (619.25–1249.50)	0.005* $p_{Switchers–Continuers}$=0.006 $p_{Switchers–Stoppers}$=0.006
FEV_1, %, M±SD (95% CI)	63.46±21.18 (59.53–67.39)	61.95±20.86 (57.34–66.56)	61.02±21.47 (50.67–71.37)	75.51±20.12 (63.89–87.12)	0.073

Note. BMI: body mass index; CRSwNP: chronic rhinosinusitis with nasal polyps; CRSsNP: chronic rhinosinusitis without nasal polyps; NSAIDs: nonsteroidal anti-inflammatory drugs; FEV_1: forced expiratory volume in the first second; AD: Atopic dermatitis.

criterion, with Holm correction as a posthoc method, were conducted when comparing three or more groups associated with a quantitative variable displayed a non-normal distribution. Frequencies in the analysis of multifield contingency tables were compared using Pearson's chi-square test.

RESULTS

Objects (participants) of the study and main results

1. Description of groups and predictors of drug withdrawal and switching

Of the 116 patients, 70.7% (*n*=82) were patients continuing treatment, 17.2% (*n*=20) stopped treatment, and 12.1% (*n*=14) switched between biologics. When comparing groups according to the main demographic and clinical characteristics, the onset of BA occurred earlier in stoppers than in continuers and switchers (*p*=0.027). Stoppers were less likely to suffer from CRSwNP (*p*=0.017). The peripheral blood eosinophil count was initially higher in switchers than in continuers and stoppers (*p*=0.005).

2. Phenotypes and biologics

Among all patients, 49.1% (*n*=57) had nonallergic eosinophilic SA, 34.5% (*n*=40) had allergic SA, and 16.4% (*n*=19) had mixed SA. A similar distribution was observed in continuers and switchers. An equal number of stoppers had allergic and nonallergic asthma (Table 2). In continuers and stoppers, patients receiving omalizumab (34.1% and 50.0%, respectively), dupilumab (25.6% and 30.0%, respectively), and

Table 2. Distribution of patients in the study groups by phenotypes and drugs received

Indicator		Total *n*=116	Group 1 Continuers *n*=82	Group 2 Stoppers *n*=20	Group 3 Switchers *n*=14
Asthma phenotypes	J45.0 allergic, *n* (%)	40 (34.5)	29 (35.4)	8 (40.0)	3 (21.4)
	J45.1 nonallergic, *n* (%)	57 (49.1)	41 (50.0)	8 (40.0)	8 (57.1)
	J45.8 mixed, *n* (%)	19 (16.4)	12 (14.6)	4 (20.0)	3 (21.4)
Biologics	Omalizumab, *n* (%)	43 (37.1)	28 (34.1)	10 (50.0)	5 (35.7)
	Benralizumab, *n* (%)	16 (13.8)	11 (13.4)	0 (0.0)	5 (35.7)
	Dupilumab, *n* (%)	27 (23.3)	21 (25.6)	6 (30.0)	0 (0.0)
	Mepolizumab, *n* (%)	23 (19.8)	16 (19.5)	4 (20.0)	3 (21.4)
	Reslizumab, *n* (%)	7 (6.0)	6 (7.3)	0 (0.0)	1 (7.1)

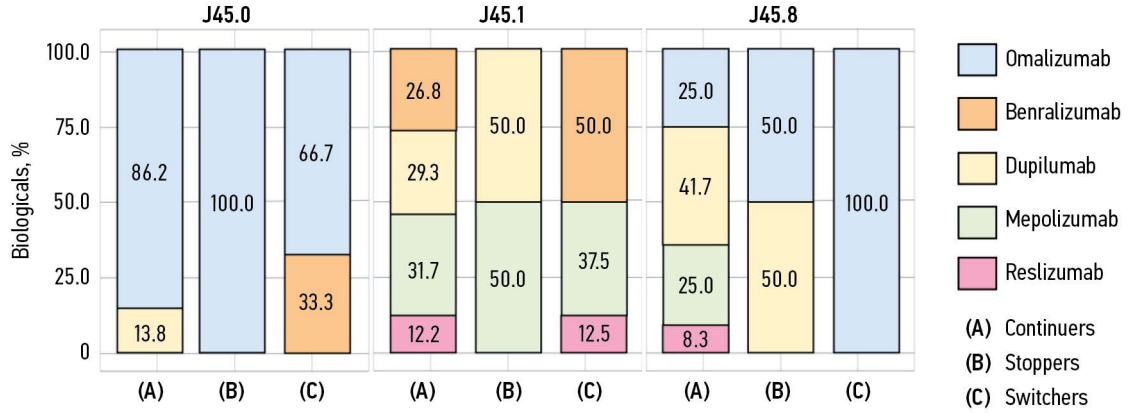

Fig. 2. Distribution of drugs in the study groups by phenotypes.
Note. J45.0: allergic severe bronchial asthma (SA); J45.1: nonallergic eosinophilic SA; J45.8: mixed SA.

mepolizumab (19.5% and 20.0%, respectively) predominated. Most stoppers received benralizumab and omalizumab (37.5% of each drug) and mepolizumab (21.4%) (Table 2).

Allergic SA phenotype. The patients in group 1 with an allergic SA phenotype continued to be treated with omalizumab (*n*=25) and dupilumab (*n*=4). In group 2, patients stopped treatment only with omalizumab (*n*=8; Fig. 2). In group 2, therapy was stopped in 3 (37.5%) patients with allergic SA for personal reasons; 2 patients (25%) who achieved asthma control (patients decided to stop therapy after 10 and 35 months of it); and in 1 patient (12.5%) because of an undesirable event (phlebothrombosis not associated with targeted therapy), ineffectiveness against asthma, and organizational reason (moving to another area). Therapy was switched from omalizumab (*n*=2) to benralizumab (*n*=1) in group 3 (Fig. 2). In patients with an allergic SA phenotype, switching was only because of the ineffectiveness of the drugs: first case, the ineffectiveness of omalizumab in relation to concomitant CRSwNP (asthma control was achieved); second case, ineffectiveness of omalizumab against SA (but remission was achieved for chronic spontaneous urticaria); and third case, ineffectiveness of benralizumab against both SA and CRSwNP. All three patients switched to dupilumab.

Nonallergic eosinophilic SA. Mepolizumab (*n*=13), dupilumab (*n*=12), benralizumab (*n*=11), and reslizumab (*n*=5) continued to be administered in group 1 among patients with nonallergic eosinophilic SA. Group 2 stopped therapy with dupilumab (*n*=4) and mepolizumab (*n*=4) (Fig. 2). Therapy was terminated in 4 (50%) patients as they refused for personal reasons, 1 patient (12.5%) because of AEs (taste in the mouth and dizziness), 1 patient (12.5%) for organizational reasons, and 2 patients because of their deaths (death from acute heart failure and from status asthmaticus in the surgical department after NSAIDs). Patients were switched from benralizumab (*n*=4), mepolizumab (*n*=3), and reslizumab (*n*=1) in group 3 (Fig. 2). Biologic was switched because of ineffectiveness against SA (*n*=4, 50%), ineffectiveness against CRSwNP (*n*=1, 12.5%), ineffectiveness against SA + CRSwNP (*n*=2, 25%), and organizational reasons ((*n*=1, 12.5%; the hospital did not purchase GEBD). Switching occurred in all dupilumab cases.

Mixed SA phenotypes. Patients with mixed asthma in group 1 continued treatment with dupilumab (*n*=5), omalizumab and mepolizumab (*n*=3), and reslizumab (*n*=1). In group 2, two patients stopped treatment with omalizumab and dupilumab (Fig. 2). The reasons for treatment termination were personal reasons (preparation for pregnancy, *n*=2,

Table 3. Reasons for stopping and first-line discontinued biologicals in patients of groups 2 and 3

Reasons for stopping and switching	Total	Therapy status		Biologics				
		stoppers	switchers	oma	benra	dupi	mepo	resli
Personal patient reasons, *n* (%)	9 (26.5)	9 (45.0)	0 (0.0)	4 (26.7)	0 (0.0)	3 (50.0)	2 (28.6)	0 (0.0)
Achieving asthma control, *n* (%)	2 (5.9)	2 (10.0)	0 (0.0)	2 (13.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
AEs, *n* (%)	3 (8.8)	3 (15.0)	0 (0.0)	1 (6.7)	0 (0.0)	1 (16.7)	1 (14.3)	0 (0.0)
Ineffectiveness against asthma, *n* (%)	8 (23.5)	1 (5.0)	7 (50.0)	4 (26.7)	2 (40.0)	0 (0.0)	2 (28.6)	0 (0.0)
Ineffectiveness against CRSwNP, *n* (%)	4 (11.8)	1 (5.0)	3 (21.4)	3 (20.0)	1 (20.0)	0 (0.0)	0 (0.0)	0 (0.0)
Ineffectiveness against asthma + CRSwNP, *n* (%)	3 (8.8)	0 (0.0)	3 (21.4)	0 (0.0)	2 (40.0)	0 (0.0)	1 (14.3)	0 (0.0)
Organizational reasons, *n* (%)	3 (8.8)	2 (10.0)	1 (7.1)	1 (6.7)	0 (0.0)	1 (16.7)	0 (0.0)	1 (100.0)
Death, *n* (%)	2 (5.9)	2 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	1 (14.3)	0 (0.0)

Note. AE — adverse event, CRSwNP — chronic rhinosinusitis with nasal polyps, oma — omalizumab, benra — benralizumab, dupi — dupilumab, mepo — mepolizumab, resli — reslizumab.

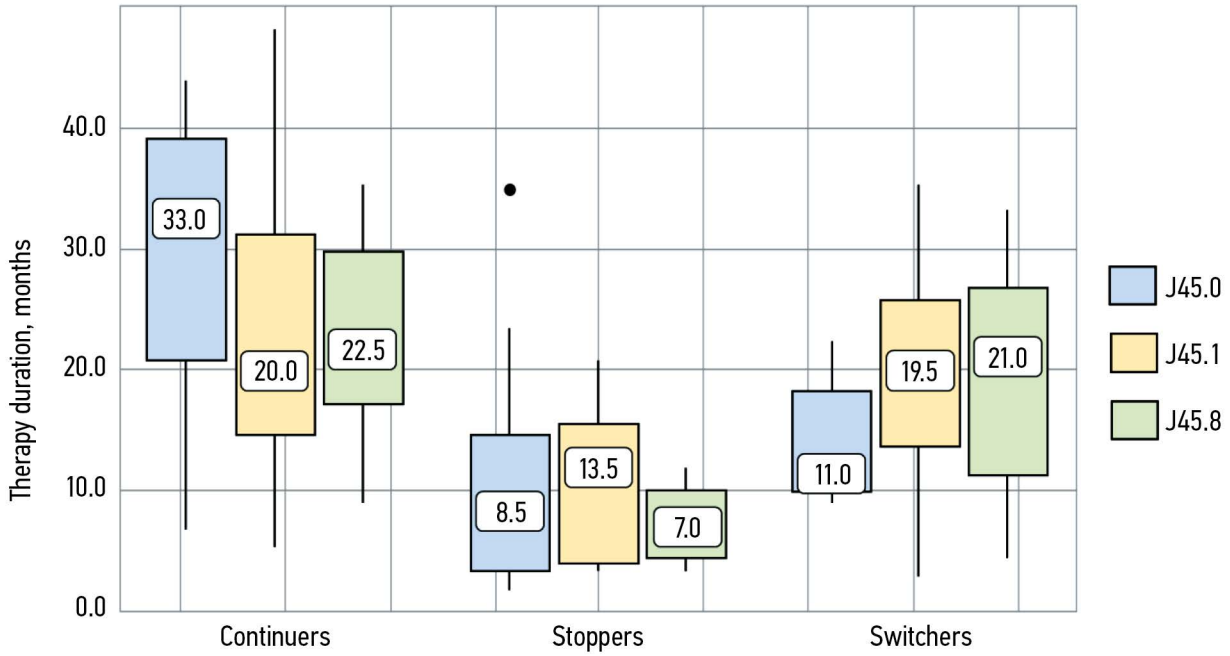

Fig. 3. Therapy duration in the observation groups depending on the asthma phenotype.
Note. J45.0: allergic SA; J45.1: nonallergic eosinophilic SA; J45.8 : mixed SA.

50%)), an adverse event on dupilumab (conjunctivitis and arthralgia, *n*=1, 25%), and ineffectiveness against CRSwNP (*n*=1, 25%). Group 3 switched only from omalizumab (*n*=3) (Fig. 2). Patients switched to dupilumab because of ineffectiveness against SA (*n*=2, 66.7%) and CRSwNP (asthma control achieved; *n*=1, 33.3%).

Additional results

3. Analysis of the stopping and switching of targeted therapy

The most common reason for stopping or switching between biologics was the ineffectiveness of therapy (combined ineffectiveness against asthma and concomitant T2 diseases), which accounted for 44.1% of all reasons for discontinuation/switching of biologics. Seven patients received omalizumab, 5 received benralizumab, and 3 received mepolizumab out of the 15 failures. No failures were noted with dupilumab and reslizumab. Only 2 of the 15 patients with ineffective initial therapy refused to switch. Thirteen patients were switched to another drug (Table 3).

Biologic discontinuation because of the achievement of asthma control was registered in two cases of omalizumab intake. AEs leading to drug withdrawal were reported in three patients, namely, thrombocytopenia with omalizumab and arthralgia, conjunctivitis, mepolizumab, acetone taste, and dizziness with dupilumab. Two patients treated with dupilumab and mepolizumab died during the study. The causes of death are described above. Deaths were unrelated to the use of biologics (Table 3).

Overall, the mean duration of targeted therapy was 21.00 (Q_1–Q_3: 12.00–32.00) months. Therapy duration did not differ significantly between the groups of continuers and switchers: 24.50 (Q_1–Q_3: 15.25–32.75) and 19.50 (Q_1–Q_3: 9.50–23.00) months, respectively (p=0.091). Stoppers received biologics significantly less, i.e., 9.50 (Q_1–Q_3: 4.00–14.25) months (p <0.001). A similar distribution according to the duration of GEBD intake (the longest duration of therapy in continuers and the shortest intake in stoppers) was observed when considering groups by phenotypes (Fig. 3). No statistically significant differences were found in therapy duration for each drug in the study period: benralizumab lasted 15.5 (Q_1–Q_3: 8.75–22.50) months, dupilumab for 18.00 (Q_1–Q_3: 10.00–29.00), mepolizumab for 21.00 (Q_1–Q_3, 16.50–30.50) months, omalizumab for 23.00 (Q_1–Q_3: 12.00–35.00), and reslizumab for 26.00 (Q_1–Q_3: 12.00–28.50) (p=0.268).

4. Schemes and the effectiveness of switching

All patients (n=14) in group 3 were switched to dupilumab: 5 patients from omalizumab and the same number from benralizumab, 3 from mepolizumab, and 1 from reslizumab (Table 4). The patient was transferred from reslizumab for organizational reasons, and all the rest were due to the ineffectiveness of the therapy against SA and/or concomitant T2 diseases.

The duration of therapy before switching was as follows: benralizumab, 9 (Q_1–Q_3: 7–16) months; omalizumab, 21 (Q_1–Q_3: 11–23) months; mepolizumab, 23 (Q_1–Q_3: 22–29) months; and reslizumab, 33 (Q_1–Q_3: 33–33.50) months (p=0.082). In 4 out of 5 patients treated with omalizumab who switched, a positive clinical effect was initially recorded, and the durations of therapy were 11, 21, 23, and 33 months, respectively. One patient did not respond with an improvement in clinical and functional parameters to omalizumab therapy (therapy duration of 6 months). Mepolizumab initially showed good effectiveness with subsequent effect fading. The lengths of mepolizumab therapy in group 3 were 21, 23, and 35 months. Moreover, 2 of 5 patients on benralizumab had a good response, with a subsequent decrease in the clinical effect at the 16th and 18th months of therapy. Furthermore, 3 of 5 patients (durations of therapy 3, 7, and 9 months) did not show a response to benralizumab.

As of April 2023, all patients (n=14) in group 3 completed the evaluation visit in the 4th month, and 8 out of 14 patients completed 12th month visit after switching to an alternative drug. Statistically significant improvements were observed in ACT, FEV_1, AQLQ, and SNOT-22 4 months after switching (Table 5). Positive dynamics persisted according to ACT and AQLQ by the 12th month of therapy, whereas FEV_1 slightly decreased. The SNOT-22 scores continued to decline by the 12th month but without statistical significance. A decrease in the proportion of patients requiring SGCS was registered at the 4th month of therapy without statistical significance; SGCS was not needed in patients who received the second-line drug for a year (p=0.050) (Table 5).

Table 4. Schemes for switching targeted therapy in group 3

Scheme of switching	Group 3 Switchers, *n* (%)		
	J45.0	J45.1	J45.8
Oma→dupi	2 (66.7)	0 (0.0)	3 (100.0)
Benra→dupi	1 (33.3)	4 (50.0)	0 (0.0)
Mepo→dupi	0 (0.0)	3 (37.5)	0 (0.0)
Resli→dupi	0 (0.0)	1 (12.5)	0 (0.0)

Note. Oma: omalizumab; dupi: dupilumab; benra: benralizumab; mepo: mepolizumab; resli: reslizumab; J45.0: allergic bronchial asthma; J45.1: nonallergic eosinophilic bronchial asthma; J45.8: mixed bronchial asthma.

Strong asthma control was achieved in 42.9% (n=6) of the patients (without considering FEV_1) and 35.7% (n=5) (considering FEV_1) at month 4. At month 12, strong control without considering FEV_1 was registered in 62.5% (n=5) of the patients, considering FEV_1 in 50% (n=4) (Table 6).

The switching reason for six patients was the ineffectiveness of the first biologic against comorbidity (CRSwNP). Five of these six patients (patients 2, 7, 9, 10, and 14) had fairly pronounced positive dynamics of nasal symptoms according to the SNOT-22 questionnaire and VAS after switching. They also managed to achieve SA control. No change in nasal symptoms was noted during 4 months of therapy (after switching) in patient 1 (Table 6).

DISCUSSION

In this study, we determined the risk factors for switching biologics and the main reasons for stopping therapy and switching from one biologic to another. A low switching rate was obtained in our registry (12.1%) comparable to the data provided by Menzies-Gow et al. (11%) [4]. Menzies-Gow et al. noted the low switching rate and suggested that perhaps a really careful selection of the first drug based on clinical characteristics and biomarkers may lead to a good response. However, the reason for the low number of switches may also be the satisfaction of the patient and doctor with the low response thresholds (e.g., a 50% reduction in exacerbations or in maintenance dose of SGCS), the fear of losing a slight improvement when switching between biologics, and insufficient information at the moment on switching effectiveness.

In a study by Menzies-Gow et al., as in our work, most switching cases related to inefficiency occurred within 12 months of starting therapy. The Global Initiative for Asthma recommends a treatment period of 4–6 months before initial response assessment, whereas patients with an intermediate or unclear response may require an extension of 6–12 months [13, 14]. However, as Menzies-Gow et al. noted, differences in switching time may be caused by regional and national restrictions on the assignment and switching of biologics [4].

Japanese researchers reported that the proportion of switched patients was 35% and 31% [15, 16]. Numata et al.

Table 5. Effectiveness rates of a second-line targeted drug for the treatment of SA

Indicator	Number of patients	Исходно, на старте препарата переключения	4th month	12th month	*p*
ACT, scores, Me (Q_1–Q_3)	14	11.00 (10.00–14.00)	19.00 (15.00–20.00)	-	0.002*
	8	11.00 (8.00–11.00)	19.50 (18.25–21.50)	20.50 (18.50–24.00)	0.015*
FEV_1, %, M±SD (95% CI)	14	65.54±22.54 (51.91–79.16)	84.62±19.83 (72.63–96.60)	-	0.006*
	8	61.67±26.47 (33.89–89.45)	86.17±16.41 (68.94–103.39)	82.83±23.96 (57.69–107.98)	0.051
AQLQ, scores, M±SD (95% CI)	14	3.69±1.14 (2.99–4.38)	4.98±1.05 (4.35–5.62)	-	0.001*
	8	3.66±0.91 (2.71–4.61)	5.19±0.95 (4.20–6.19)	5.58±1.17 (4.36–6.81)	0.019*
Percentage of patients requiring SGCS	14	57.1	14.3	-	0.058
	8	50.0	0.0	0.0	0.050*
SNOT-22, scores, Me (Q_1–Q_3)	14	55.0 (39.0–62.0)	36.0 (26.0–54.0)	-	0.012*
	8	63.5 (53.0–89.0)	49.0 (27.5–55.5)	33.0 (20.8–38.5)	0.154

Note. ACT: Asthma Control Test; FEV_1: forced expiratory volume in the first second; AQLQ: Asthma Quality of Life Questionnaire; SGCS: systemic glucocorticosteroids; *statistically significant difference (p <0.05).

described the selection of the first-line drug based on biomarkers (total IgE, blood eosinophils, and FeNO) without considering the clinical picture. For example, out of 35 patients who were prescribed omalizumab, 7 patients tested negative for all biomarkers, 11 patients exhibited elevated eosinophils and total IgE levels, and 4 patients displayed elevated levels for all 3 biomarkers [15]. The patients who had tested negative for biomarkers had T2 low asthma. Patients who tested positive for 2–3 biomarkers may have had nonallergic eosinophilic or mixed asthma. Accordingly, the choice of omalizumab as a first-line drug in these cases raises questions. Matsumoto-Sasaki et al. failed to provide a detailed description of the first biologic choice. However, the presence of atopy was confirmed by presence of a specific IgE to at least one inhaled allergen (it is unclear whether the allergen exposure was considered with the occurrence of clinical symptoms) and that the diagnosis of allergic rhinitis was made by a general practitioner or an otolaryngologist based on a positive response to the question, "Do you have any nasal allergies, including hay fever?" [16].

The issue of phenotyping and endotyping for selecting GEBD remains relevant, starting from the advent of the first targeted drug. This is shown by the OSMO study, wherein patients initially treated with omalizumab and who did not achieve asthma control were switched to mepolizumab with positive dynamics. The authors confirmed that indications for the appointment of omalizumab were unknown for all patients because this was before the beginning of the study [2]. Most likely, during the period when only omalizumab was available, its administration in some cases was made to patients with eosinophilic asthma without a clinically significant allergic component.

Other researchers have also argued that targeted drugs with different mechanisms of action can be prescribed to some patients. Japanese authors have indicated that 30% of the patients with SA had overlapping indications for four biologics (omalizumab, mepolizumab, benralizumab, and dupilumab), and 75% of the patients with SA could be prescribed two or more biologics [9,17].

Albers et al. concluded that 27–37% of patients were eligible for treatment with omalizumab among patients eligible for treatment with mepolizumab (n=101) [18].

In our opinion, the choice of a targeted drug in patients with an allergic phenotype is the least difficult. The first line is usually an anti–IgE drug. If selecting a dose of omalizumab is impossible or if SA is combined with AD, dupilumab becomes the drug of choice. Therapy switching in allergic asthma more often occurs because of the fading of the omalizumab effect (Fig. 4).

The choice of the targeted therapy in nonallergic eosinophilic asthma is usually between anti–IL5 and anti-IL4R,13; moreover, apart from the indications of steroid dependence for dupilumab and an eosinophil level of ⩾400 cells/μL for reslizumab, specific indications are not described in the instructions for biologics or in the literature (Fig. 4).

Mixed asthma is the most difficult in terms of choosing a class of GEBD because the choice based on the predominance of the clinical or laboratory component of the phenotype does not always ensure therapy effectiveness. Omalizumab was initially prescribed to 8 patients with mixed asthma. Four of the 8 patients had late-onset asthma, and omalizumab was ineffective in these 4 patients Therefore, patients with mixed asthma should have an early onset of asthma (<20 years according to our registry) to be prescribed omalizumab. Anti–IL5 drugs were prescribed for patients with mixed asthma having eosinophilia of ⩾1.000 cells/μL, while there were no withdrawals or switching from mepolizumab and reslizumab in mixed asthma (benralizumab was not prescribed to anyone with the J45.8 phenotype). The range

Table 6. Characteristics of patients switching between biologics

N	Sex	Age, years	Asthma phenotype	First GEBD	Duration of the first GEBD intake, months	Switching reasons	Duration of taking dupilumab as a switch drug as of April 2023	Dynamics after switching to dupilumab					
								Strong control with FEV_1		Strong control without FEV_1		Dynamics of SNOT-22	Dynamics in the VAS
								4th month	12th month	4th month	12th month		
1	M	58	J45.1	Mepolizumab	35	Ineffectiveness against asthma + CRSwNP	5	no	-	no	-	- 1 score at the 4th month	+ 4 scores in the 4th month
2	M	46	J45.0	Omalizumab	23	Ineffectiveness against CRSwNP	12	no	yes	no	yes	- 23 scores at the 12th Month	- 5 scores at the 12th month
3	F	51	J45.1	Reslizumab	33	Organizational reason	12	no	no	no	no		
4	F	55	J45.1	Mepolizumab	21	Ineffectiveness against asthma	8	yes	-	yes	-		
5	F	68	J45.8	Omalizumab	21	Ineffectiveness against asthma	17	no	no	no	no		
6	F	52	J45.0	Omalizumab	11	Ineffectiveness against asthma	12	no	no	yes	yes		
7	F	59	J45.8	Omalizumab	33	Ineffectiveness against CRSwNP	5	yes	-	yes	-	- 35 scores at the 4th month	- 9 scores at the 4th month
8	F	47	J45.8	Omalizumab	6	Ineffectiveness against asthma	22	yes	yes	yes	yes		
9	F	35	J45.1	Benralizumab	3	Ineffectiveness against CRSwNP	21	yes	yes	yes	yes	- 69 scores at the 12th month	- 4 scores at the 12th month
10	F	54	J45.1	Benralizumab	18	Ineffectiveness against asthma + CRSwNP	15	no	yes	no	yes	- 16 scores at the 12th month	- 6 scores at the 12th month
11	F	65	J45.1	Mepolizumab	23	Ineffectiveness against asthma	3	no	-	no	-		
12	F	58	J45.1	Benralizumab	16	Ineffectiveness against asthma	12	no	no	no	no		
13	F	58	J45.1	Benralizumab	7	Ineffectiveness against asthma	3	no	-	no	-		
14	F	49	J45.0	Benralizumab	9	Ineffectiveness against asthma + CRSwNP	5	yes	-	yes	-	- 10 scores at the 4th month	- 1 score at the 4th month

Note. M — male, F — female.

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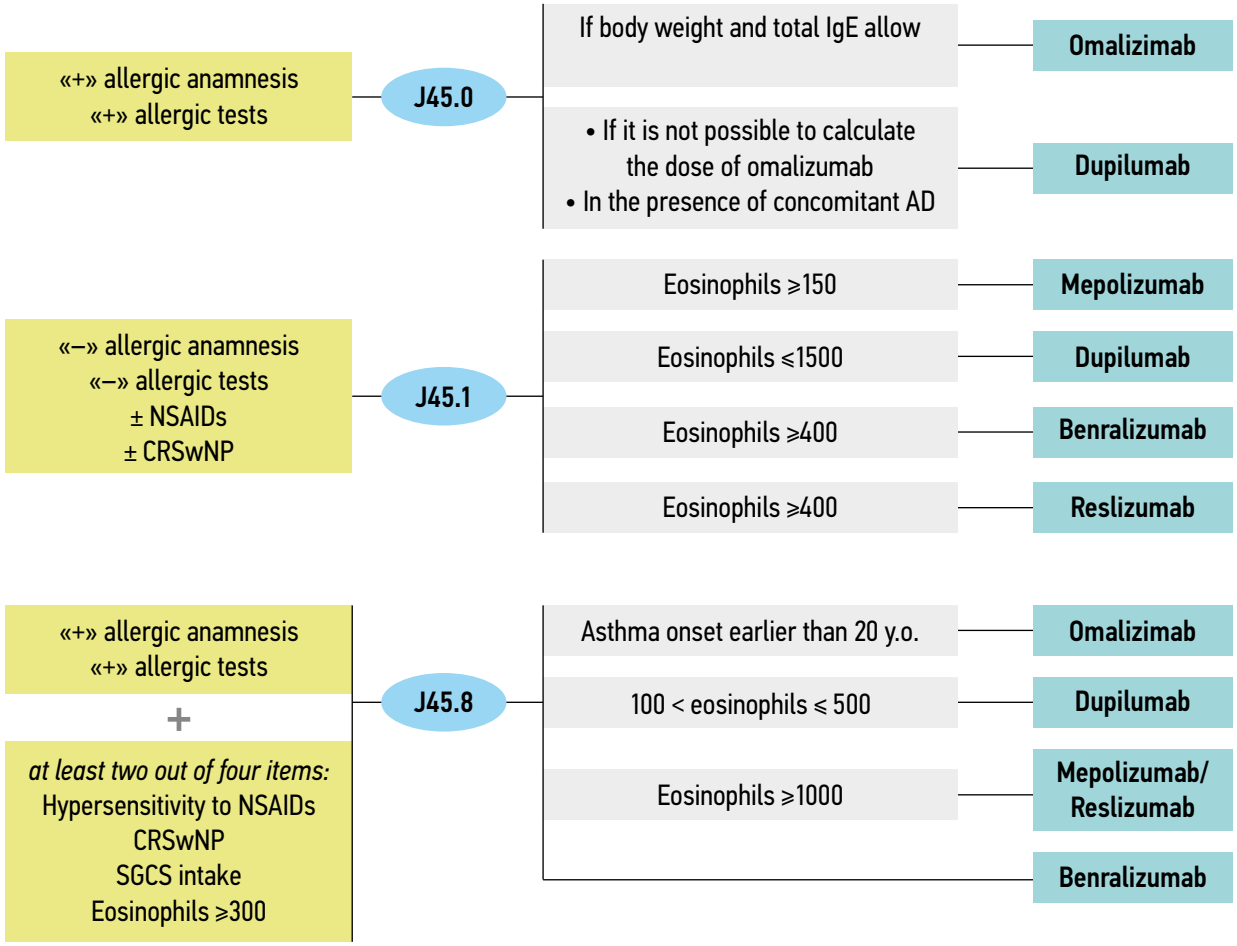

Fig. 4. Scheme for choosing an initial biologic for patients with severe bronchial asthma.
Note. NSAIDs: nonsteroidal anti-inflammatory drugs; CRSwNP: chronic rhinosinusitis with nasal polyps; SGCS: systemic glucocorticosteroids; AD: atopic dermatitis. The diagram presents combined data based on clinical recommendations for targeted therapy of SA and our observations of therapy effectiveness in patients with SA in the Sverdlovsk region registry.

of peripheral blood eosinophils in patients with mixed asthma who were prescribed dupilumab as the first-line drug ranged from 110 to 500 cells/mcL (there were no switches in this group; however, there was drug withdrawal because of the side effects of "conjunctivitis," and "arthralgia" in a patient with a combination of SA + AD and in another patient for personal reasons) (Fig. 4). These assumptions require further observations with several patients.

The difficulty of choosing the first drug in nonallergic eosinophilic and mixed asthma is confirmed by the higher proportion of switched patients among mixed and nonallergic eosinophilic asthma than among allergic asthma (15.8%=3 out of 19, 14%=8 out of 57, and 7.5%=3 out of 40, respectively) in our study.

We obtained a significant predominance of patients with a combination of SA and CRSwNP in groups 1 (continued) and 3 (switched) compared with group 2. The combination of SA and CRSwNP significantly reduced patients' quality of life [19]. The severe suffering caused by the combination of diseases probably leads to greater adherence to the treatment of patients in groups 1 and 3. Group #2 (stoppers) more often refused therapy for personal reasons.

Eosinophil levels are considered when prescribing anti-IL5 drugs because of the mechanism of action of this group. However, not all patients have a high eosinophil level as a predictor of a good response, particularly to benralizumab. Of the 14 patients in group 3, 9 were initially prescribed anti–IL5 drugs (1 reslizumab, 3 mepolizumab, and 5 benralizumab). The patient was switched from reslizumab because of problems with drug purchase. Three patients on mepolizumab initially had a good response to therapy with subsequent fading of effect (therapy duration before switching was 21, 23, and 35 months). Two out of five patients on benralizumab (baseline eosinophil levels of 2,330 and 1,500 cells/mcL, respectively) also had a good response with a subsequent decrease in the clinical effect at the 16th and 18th months of therapy. However, no response to therapy was noted in 3 of 5 patients, despite the initial levels of eosinophils of 776, 950, and 1995 cells/μL. We planned to achieve SA and concomitant CRSwNP control by prescribing anti–IL5 drugs to patients with high eosinophilia. This may explain why the eosinophil level was higher in switchers than in continuers and stoppers. However, even foreign authors noted that high eosinophilia is a predictor of switching between targeted drugs [4, 20].

According to foreign authors, in addition to high eosinophilia, predictive factors for future switching are frequent exacerbations and frequent use of healthcare resources before the initiation of the first targeted therapy drug [4, 20].

Patients were switched to dupilumab because this drug blocks the mechanisms of allergic and nonallergic eosinophilic asthma; in our opinion, this is the drug of choice in case of "failure" of anti–IgE and anti–IL5 strategies at the start. This tactic proved effective because the patients achieved control (ACT scores, 20.50 [Q_1–Q_3, 18.50–24.00] and FEV_1 increased to 82.83% ± 23.96% [95% CI 57, 69–107.98]), improved their quality of life, no longer required SGCS, and experienced reduced nasal symptoms (SNOT-22) by the 12th month of therapy.

Achievement of SA remission is currently a debatable topic. In 2020, Menzies-Gow et al. proposed that if a patient demonstrated the following conditions: the absence of significant asthma symptoms (evaluated using validated instruments), improvement and stabilization of lung function, agreement with their doctor to achieve remission, and nonrequirement of SGCS (for treating exacerbations and maintaining asthma control) for ⩾12 months, then they were said to experience complete remission of SA [21]. We observed patients in the study for only 12 months to assess the effectiveness of switching. Therefore, we used the modified combined indicator "strong asthma control," which included the absence of asthma exacerbations, nonrequirement of SGCS, ACT scores ⩾20, and FEV_1 ⩾80%. Moreover, 62.5% and 50% of the patients achieved strong control of asthma without and with consideration of FEV_1, respectively. According to Numata et al., switching effectiveness (determined by GETE) was noted in 32% (11 out of 34) of patients [15]. Abbas et al. reported that approximately 26% (29 of 112 patients) who switched between biologics experienced a 40% reduction in the number of clinically significant exacerbations (from 3.46 to 2.07, p=0.01); these patients also significantly improved FEV_1 (330 mL, p=0.01) and ACT scores (3, p=0.04). Furthermore, 36% patients were able to stop taking SGCS [22].

Moreover, we would like to note the importance of doctors from any specialty performing anamnesis on drug hypersensitivity. The combination of SA with CRSwNP in a patient should be considered in terms of intolerance to aspirin. The patient, who died in the surgical department after the administration of NSAIDs, suffered from SA + CRSwNP and had a history of hypersensitivity to NSAIDs.

Study limitations

The limitations of this study are related to the "nonideal" conditions of real clinical practice, small sample size, and some switching arbitrariness because of the lack of recommended schemes for switching between GEBDs.

CONCLUSION

According to our data, targeted therapy in patients with SA in real clinical practice is accompanied by stopping therapy (17.2% of cases) and switching between biologics (12.1% of cases). The reasons for the discontinuation of GEBDs were as follows: personal reasons (45%), AEs (15%), achievement of asthma control (10%), organizational reasons (10%), death (10%), and ineffectiveness against SA (5%) and CRSwNP (5%). Patients who completed targeted therapy were less likely to suffer from CRSwNP; the asthma onset in these patients occurred earlier compared to that in patients who continued treatment and switched biologics. The reasons for changing GEBD were as follows: ineffectiveness against SA (50%), CRSwNP (21.4%), SA and CRSwNP combined (21.4%), and organizational reasons (7.1%). The main reason for switching was the ineffectiveness of the therapy against SA and/or concomitant T2 diseases. The starting drugs were omalizumab and benralizumab in most switched cases. Dupilumab was an alternate GEBD when switching biologics. Furthermore, switching the starting GEBD, which was aimed only at blocking eosinophils or IgE, (because of its ineffectiveness in some patients) to a drug with a dual mechanism of action (suppression of IgE production and eosinophilic inflammation) resulted in a significant improvement in ACT, FEV_1, AQLQ, and a decrease in the severity of concomitant nasal symptoms (SNOT-22) as well as nonrequirement of SGCS.

ADDITIONAL INFORMATION

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