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Steroid-sparing benefits of biologic use in hypereosinophilic syndrome and substantial disease burden across subtypes

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Background: Limited data exist on the burden of myeloproliferative, lymphocytic and idiopathic subtypes of hypereosinophilic syndrome (M-HES, L-HES and I-HES) and the characteristics of patients with HES receiving biologic therapies. This analysis aimed to further characterize these subtypes and explore the impact of biologics in a real-world European setting.

Methods: This was a *post hoc* subgroup analysis of a retrospective, non-interventional, chart review (GSK ID: 214657) across five European countries. Index date was first clinical visit during January 2015–December 2019 (after or at time of HES diagnosis). Patients with HES aged ≥ 6 years with ≥ 1 -year follow-up from index were included. Demographics, disease characteristics, diagnostic assessments, comorbidities, types of treatment, clinical manifestations, clinical outcomes and HES-related healthcare resource utilization were summarized for HES overall and subtypes. Oral corticosteroid (OCS) use and clinical manifestations/outcomes were assessed 12-months pre- and post-biologics.

Results: The analysis included 280 patients with I-HES ($n = 155$), M-HES ($n = 66$), L-HES ($n = 42$) and chronic eosinophilic leukemia ($n = 2$). The most common clinical manifestations were fatigue (54.2% I-HES, 52.4% L-HES, 42.4% M-HES), skin itch (36.4% M-HES, 35.7% L-HES, 33.5% I-HES) and pain (31.0% L-HES, 30.3% M-HES, 27.1% I-HES). Biologic use was highest with L-HES (64.3%), followed by I-HES (43.9%) and M-HES (34.8%). Clinical response rates were highest for the I-HES subtype (75.5%; 66.7% L-HES, 63.6% M-HES). Hospitalizations were highest for L-HES (45.2%; 30.3% M-HES, 25.8% I-HES). The annualized rate of OCS prescriptions reduced by 56.8% (0.44–0.19 per person-year) and the proportion of patients with ≥ 1 clinical response increased 3.6-fold (6.5%–23.4%) between the pre- and post-biologics periods.

Conclusions: All HES subtypes had a substantial disease burden and were commonly associated with fatigue, skin itch and pain. I-HES appeared to be more responsive to treatment than L-HES and M-HES. Biologic use for HES led to more patients experiencing clinical responses and was OCS-sparing.

KEYWORDS

hypereosinophilic syndrome, burden of disease, biologics, mepolizumab, retrospective study, corticosteroid

1 Introduction

Hypereosinophilic syndromes (HES) are rare and heterogeneous blood disorders characterized by persistent hypereosinophilia ($>1,500$ cells/ μ l) and eosinophilic tissue infiltration leading to organ damage (1–3). HES prevalence has been estimated to be 1.5 cases per 100,000 people in Europe (4), but regional estimates vary (North America: 0.32–6.3 cases per 100,000; UK: 0.15–0.89 cases per 100,000) (5, 6). HES is diagnosed when known causes of secondary hypereosinophilia are excluded (1, 3, 7, 8) and can be classified into several subtypes, including myeloproliferative, lymphocytic and idiopathic variants (M-HES, L-HES and I-HES, respectively), based on distinct molecular characteristics (1, 3, 7, 9).

M-HES is diagnosed in patients whose hypereosinophilia is caused by a defined myeloid malignancy or who have clinical characteristics consistent with one (7). L-HES is a form of reactive HES, diagnosed when patients present with an aberrant immunophenotype in ≥ 1 T-cell subset, increased type 2 cytokine production and signs of HES-related organ damage; clonal T-cell receptor gene rearrangement may or may not be evident (3). I-HES is a diagnosis of exclusion, made when the criteria for HES are fulfilled and all known primary and secondary causes of hypereosinophilia have been excluded (1).

HES-related disease flares, defined as a period of worsening of HES-related symptoms, have a significant adverse impact on health and quality of life and may be life-threatening. The goals of HES treatment are to control disease symptoms and minimize tissue damage (10). Therapy typically relies on high-dose maintenance oral corticosteroids (OCS), while immunosuppressant and/or cytotoxic therapies may be added for OCS-resistant HES (11). OCS can be associated with adverse effects and may be less effective in patients with M-HES and L-HES (11–13). In the first-line setting, M-HES may also be treated with tyrosine kinase inhibitors such as imatinib (14). Several biologics have demonstrated reductions in circulating eosinophils resulting in clinical benefits (14, 15). Mepolizumab is a biologic targeting interleukin (IL)-5, which is approved in Europe and the US for inadequately-controlled HES without an identifiable non-hematologic cause (16, 17). In a Phase III trial, mepolizumab was associated with a statistically significant reduction in the proportion of patients experiencing flares, or having to withdraw from the trial, vs. placebo (18). Targeted therapies, such as mepolizumab, can contribute to OCS-sparing strategies and could improve clinical outcomes for patients (19–21).

A retrospective, non-interventional study of patients with HES from France, Germany, Italy, Spain and the UK, identified a substantial disease burden including comorbidities such as asthma, anxiety or depression, hypertension and chronic sinusitis with nasal polyps (22). Additionally, high rates of healthcare resource utilization (HCRU) were reported, with approximately 30% of patients requiring hospitalization, 26% requiring emergency department visits and 87% requiring outpatient visits for HES-related reasons over a median follow-up of 2.4 years (22). These findings highlight the need for optimized HES management strategies.

Given that HES is a rare disorder there are limited data available on clinical outcomes and treatment patterns for patients

and there are very few published studies reporting such data in patients with M-HES, L-HES or I-HES subtypes (9, 13, 23, 24). There is some evidence that symptoms differ according to subtype. For example, I-HES appears to be particularly associated with left-ventricular abnormalities, respiratory issues and gastrointestinal symptoms; M-HES with splenomegaly, anemia and fatigue; and L-HES with skin lesions/rashes and gastrointestinal symptoms (9). Additionally, there are limited data globally from clinical trials or real-world usage of emerging biologic therapies for HES and their clinical benefits, including OCS-sparing (15, 18, 19, 25, 26). Therefore, this *post hoc* subgroup analysis aimed to characterize the burden of HES by disease subtype, to gain better understanding of the characteristics of patients with HES receiving biologic therapies and to explore the clinical impact of biologic therapy in a real-world European setting.

2 Materials and methods

2.1 Study design and population

These were *post hoc* subgroup analyses of a retrospective, non-interventional, longitudinal, physician panel-based chart review study (GSK ID: 214657) of patients diagnosed with HES across five European countries (Germany, Italy, France, Spain and the UK), the methodology of which has been reported previously (22). Briefly, diagnosis date was defined as the date of HES diagnosis and index date was defined as the first clinical visit for any reason occurring between January 2015 and December 2019 (patients could have an existing diagnosis of HES or be newly diagnosed at the index date). For patients diagnosed before the index date, a pre-index period was utilized from which patient demographics and baseline clinical characteristics were identified. Follow-up included the period from index date to the earliest occurrence of death, loss to follow-up or end date of chart abstraction. The last date of follow-up was 14 July, 2021. The study included patients with a physician-confirmed HES diagnosis aged ≥ 6 years at time of diagnosis with ≥ 1 -year follow-up from index, except where follow-up ended due to death.

2.2 Data source and data collection

Longitudinal patient-level data were obtained from demographically and geographically diverse, nationally representative populations. Physicians ($N = 121$) were the primary healthcare provider for ≥ 1 eligible patient with HES, with access to their medical records. Physicians abstracted medical charts of randomly selected patients. Physicians were from different practice settings (academic or community-based) and included targeted specialties (allergy, hematology, immunology, internal medicine, pulmonology and rheumatology) from each participating country. Only anonymized data were collected. Physicians were blind to the identity of the study sponsor and vice versa.

Demographic and baseline characteristic information were obtained from patient charts from the pre-index period (between HES diagnosis and the index date for patients diagnosed before index; these characteristics were also collected for patients diagnosed at index). Clinical manifestations and outcomes of HES and HCRU were assessed from the index date until the end of follow-up. Comorbid conditions and treatment patterns were assessed from HES diagnosis until end of follow-up, unless otherwise stated.

2.3 Subgroup analysis of patient characteristics and outcomes by HES subtype

Data were summarized for the overall HES population and M-HES, L-HES and I-HES subtypes (defined *post hoc*) as follows: patient demographics and disease characteristics (including age at diagnosis, age at index and disease duration), diagnostic assessments, comorbidities, types of treatment (e.g., OCS, immunosuppressant/cytotoxic agents, biologics or other therapies), clinical manifestations, clinical outcomes and HES-related HCRU. Clinical outcomes included the occurrence of flares, defined as a worsening of HES-related symptoms or blood eosinophil counts requiring therapy escalation (dose increase or additional/new therapy) and responses to treatment. A complete response was defined as physician-reported improved or resolved symptoms and a normal eosinophil count (≤ 500 cells/ml) (27). Partial response reflected improved symptoms and eosinophil count that was improved but was not in the reference range and required more therapy.

2.4 Subgroup analysis of patients receiving biologic therapy

Demographics, disease characteristics, comorbidities and HCRU were summarized for the subgroup of patients who had received biologic treatment between HES diagnosis and end of follow-up. For patients with a non-missing date for ≥ 1 biologics prescription pre- and post-biologic initiation periods were defined. The pre-biologics period was defined as 12 months before and including the initiation of biologics. Only events and person-years after HES diagnosis were included. The post-biologics period was defined as 12 months after the initiation of biologics, or until death or end of follow-up. The following outcomes were summarized for ≤ 12 months pre- and post-biologics initiation: OCS use (annualized rate of prescriptions and proportion of patients receiving ≥ 1 prescription), clinical manifestations (proportion of patients with manifestation) and clinical outcomes (flares and clinical response to treatment).

2.5 Sample size and statistical analysis

The subgroup analyses were defined *post hoc*. All study outcomes were summarized using descriptive statistics and no

comparative testing was performed. Real-world flare-free survival (FFS) was assessed over the 6 years following the initial diagnosis date (6-year restricted mean survival time) using Kaplan–Meier analysis. Data analysis was performed using SAS Enterprise Guide Version 7.15 (SAS Institute Inc., Cary, NC, USA).

3 Results

3.1 Patient characteristics and outcomes by HES subtype

Of the 280 patients for whom data were collected, 265 had a physician-defined subtype and 15 had unknown disease subtype. Of those with a physician-defined subtype, 155 had I-HES, 66 had M-HES, 42 had L-HES and 2 had chronic eosinophilic leukemia. Overall patient demographics and physician characteristics have been published previously (22). HES subtype distribution varied between countries, although in all countries most patients had I-HES [51.9% in Spain (lowest), 61.5% in Italy (highest); 55.4% overall]. The highest proportion of patients with M-HES was in Spain (34.6%; 23.6% overall) and with L-HES was in the UK (22.6%; 15% overall).

A higher proportion of patients with M-HES were male (75.8%) and were older at diagnosis (mean age 47.0 years) than in the overall population (65.0% and 42.4 years, respectively) and other subtypes (Table 1). The median number of diagnostic assessments was similar across HES subtypes; however, types of testing performed varied according to disease subtype (Table 1). For example, allergy testing (83.3%) and kidney function testing (95.2%) were performed most frequently among patients with L-HES, whereas bone marrow aspiration and biopsy (80.3%) and molecular genetic testing (71.2%) were more frequent in patients with M-HES. Median duration of HES (2.5–2.9 years) and length of follow-up (2.3–2.5 years) were similar across subtypes. The highest median [interquartile range (IQR)] blood eosinophil count was observed in the M-HES subtype [2,300.0 (850.0, 4,500.0) cells/ μ l]; counts in L-HES and I-HES were 1,570.0 and 1,890.0 cells/ μ l, respectively (Table 1).

Asthma, anxiety or depression, nasal polyps and hypertension were the most common comorbidities across subtypes (Table 2). Asthma was most common in I-HES (52.3%) and less common in M-HES and L-HES subtypes (25.8%–47.6%, respectively). Anxiety or depression affected more patients with M-HES (48.5%) than L-HES (33.3%) or I-HES (34.2%). Nasal polyps were most common with I-HES (38.7%) and less common with the other subtypes (23.8%–27.3%); while rates of hypertension were reported in around one-third of patients (31.6%–36.4%) across subtypes (Table 2).

Mean [standard deviation (SD)] time from diagnosis to initiation of HES therapy was shortest for M-HES [0.4 (1.1) years] and longest for L-HES [1.0 (2.2) years; Table 3]. OCS were received by 80.3%–92.3% of patients across all subtypes and were most commonly used among patients with I-HES; however, the mean (SD) maximum daily OCS dose was lowest in the I-HES subtype [28.4 (19.3) mg] and highest with the M-HES

TABLE 1 Baseline patient demographics and disease characteristics across HES subtypes (22).

Patient baseline characteristics	Overall ^a (N = 280)	Myeloproliferative (N = 66)	Lymphocytic (N = 42)	Idiopathic (N = 155)
Patient country, n (%)				
France	61 (21.8)	16 (24.2)	11 (26.2)	33 (21.3)
Germany	53 (18.9)	10 (15.2)	8 (19.0)	30 (19.4)
Italy	52 (18.6)	9 (13.6)	4 (9.5)	32 (20.6)
Spain	52 (18.6)	18 (27.3)	5 (11.9)	27 (17.4)
UK	62 (22.1)	13 (19.7)	14 (33.3)	33 (21.3)
Age at HES diagnosis, years, mean (SD)	42.4 (16.2)	47.0 (16.0)	40.0 (17.9)	40.7 (15.6)
Age on index date ^b , years, mean (SD)	43.7 (15.8)	47.7 (15.7)	40.8 (17.9)	42.2 (15.1)
6–11 years, n (%)	9 (3.2)	2 (3.0)	1 (2.4)	6 (3.9)
12–17 years, n (%)	9 (3.2)	1 (1.5)	5 (11.9)	3 (1.9)
Male, n (%)	182 (65.0)	50 (75.8)	28 (66.7)	98 (63.2)
Year of diagnosis, n (%)				
2014 or before	32 (11.4)	6 (9.1)	4 (9.5)	20 (12.9)
2015–2019	248 (88.6)	60 (90.9)	38 (90.5)	135 (87.1)
Disease duration ^c , years, median (IQR)	2.7 (1.8, 4.1)	2.7 (1.9, 3.8)	2.5 (1.7, 4.1)	2.9 (1.8, 4.6)
Length of follow-up ^d , years, median (IQR)	2.4 (1.6, 3.6)	2.5 (1.7, 3.2)	2.3 (1.6, 3.5)	2.5 (1.6, 3.7)
Blood eosinophil count, cells/μl, median (IQR) ^e	1,900.0 (690.0, 3,500.0)	2,300.0 (850.0, 4,500.0)	1,570.0 (485.0, 5,500.0)	1,890.0 (790.0, 3,000.0)
Number of diagnostic assessments, median (IQR) ^f	10.0 (6.0, 12.0)	10.0 (6.0, 14.0)	10.0 (7.0, 12.0)	10.0 (6.0, 12.0)
Diagnostic assessments, n (%) ^g				
Absolute blood eosinophil count	261 (93.2)	61 (92.4)	39 (92.9)	146 (94.2)
Allergy tests to diagnose environmental or food allergies ^h	195 (69.6)	42 (63.6)	35 (83.3)	109 (70.3)
Blood tests to screen for autoimmunity	201 (71.8)	46 (69.7)	30 (71.4)	115 (74.2)
Bone marrow aspiration and biopsy	166 (59.3)	53 (80.3)	22 (52.4)	86 (55.5)
Imaging scans of affected organs ⁱ	201 (71.8)	50 (75.8)	33 (78.6)	110 (71.0)
Kidney function tests	237 (84.6)	55 (83.3)	40 (95.2)	130 (83.9)
Liver function tests	225 (80.4)	51 (77.3)	35 (83.3)	127 (81.9)
Molecular genetic tests to detect <i>FIP1L1-PDGFR</i> A or other chromosomal abnormalities ^j	147 (52.5)	47 (71.2)	18 (42.9)	78 (50.3)
Skin or other tissue biopsy	122 (43.6)	26 (39.4)	22 (52.4)	67 (43.2)
Tests to detect parasitic infection	142 (50.7)	40 (60.6)	15 (35.7)	85 (54.8)
Screening for ABPA	92 (32.9)	27 (40.9)	17 (40.5)	46 (29.7)
Other methods	3 (1.1)	2 (3.0)	1 (2.4)	0 (0.0)

ABPA, allergic bronchopulmonary aspergillosis; CT, computed tomography; EOF, end of follow-up; HES, hypereosinophilic syndrome; IQR, interquartile range; MRI, magnetic resonance imaging; SD, standard deviation.

^aOverall (N = 280) included patients with myeloproliferative (N = 66), lymphocytic (N = 42), idiopathic (N = 155), other (N = 2) and unknown (N = 15) disease subtypes.

^bIndex date was defined as the date of a patient's earliest visit with their physician between January 2015 and December 2019 on or after the patient's HES diagnosis.

^cDisease duration was calculated as the time between HES diagnosis and EOF (i.e., last physician encounter or death).

^dLength of follow-up was calculated as the time between index date and EOF (i.e., last physician encounter or death).

^eMost recent documented lab test value between diagnosis and index date. Blood eosinophil counts values available for n = 241, n = 56, n = 38, n = 133 patients from the overall, M-HES, L-HES and I-HES subtypes respectively.

^fAll categories of diagnostic assessment were counted for this statistic. For example, if a physician indicated that a patient had an imaging scan of affected organs, and then further specified that the patient had an abdominal CT and a chest radiograph, this would count as two diagnostic assessments.

^gCategories of diagnostic assessments were not mutually exclusive.

^hIncludes blood tests and allergy skin tests.

ⁱIncludes abdominal CT, chest radiograph, chest CT, sinus CT, echocardiogram, cardiac MRI, other imaging.

^jExamples of other chromosomal abnormalities include *BCR-ABL1*, *JAK2 V617F*, *KIT D816V*, clonal *T-cell* receptor rearrangements and karyotyping.

subtype [38.6 (19.0) mg; Figure 1; Table 3]. The use of immunosuppressive and cytotoxic therapies was most common among the M-HES (71.2%) and L-HES (69.0%) subtypes. This included the targeted therapy imatinib, which was used by 39.4% of patients with M-HES, 2.4% with L-HES and 17.4% with I-HES (Table 3). Biologic use was highest in patients with L-HES (64.3%), followed by I-HES (43.9%) and M-HES (34.8%). The most common biologic therapies were mepolizumab (15.4%), benralizumab (12.1%) and rituximab (12.1%). Mean (SD) time

from HES diagnosis to biologic initiation ranged from 2.7 (3.2) years for L-HES to 3.0 (3.6) years for I-HES (Table 3). The most common therapies reported as ongoing at end of follow-up were OCS in I-HES, immunosuppressants/cytotoxic therapies in M-HES and biologic therapies in L-HES (Figure 1; Supplementary Table 1).

A median (IQR) of 3.0 (1.0, 5.0) distinct clinical manifestations was observed for each HES subtype. The patterns of organ involvement varied across subtypes but constitutional, lung and

TABLE 2 Patient comorbidities across HES subtypes (assessed between HES diagnosis and end of follow-up).

Comorbidities, ^b <i>n</i> (%)	Overall ^a (<i>N</i> = 280)	Myeloproliferative (<i>N</i> = 66)	Lymphocytic (<i>N</i> = 42)	Idiopathic (<i>N</i> = 155)
Asthma	126 (45.0)	17 (25.8)	20 (47.6)	81 (52.3)
Anxiety or depression	102 (36.4)	32 (48.5)	14 (33.3)	53 (34.2)
Nasal polyps ^c	91 (32.5)	18 (27.3)	10 (23.8)	60 (38.7)
Hypertension	91 (32.5)	24 (36.4)	14 (33.3)	49 (31.6)
Vasculitis	47 (16.8)	8 (12.1)	8 (19.0)	30 (19.4)
Obesity	44 (15.7)	12 (18.2)	5 (11.9)	23 (14.8)
Lower respiratory disease(s) ^d	39 (13.9)	12 (18.2)	6 (14.3)	19 (12.3)
Diabetes	35 (12.5)	12 (18.2)	8 (19.0)	12 (7.7)
Osteoporosis	31 (11.1)	10 (15.2)	4 (9.5)	17 (11.0)
Liver disease	24 (8.6)	10 (15.2)	4 (9.5)	9 (5.8)
Glomerulonephritis	21 (7.5)	6 (9.1)	6 (14.3)	8 (5.2)
Any cancer	20 (7.1)	11 (16.7)	5 (11.9)	3 (1.9)
Cerebrovascular disease	9 (3.2)	1 (1.5)	3 (7.1)	3 (1.9)
Rheumatoid arthritis	8 (2.9)	2 (3.0)	4 (9.5)	1 (0.6)
Other ^e	8 (2.9)	2 (3.0)	2 (4.8)	3 (1.9)

COPD, chronic obstructive pulmonary disease; EOF, end of follow-up; HES, hypereosinophilic syndrome.

^aOverall (*N* = 280) included patients with myeloproliferative (*N* = 66), lymphocytic (*N* = 42), idiopathic (*N* = 155), other (*N* = 2) and unknown (*N* = 15) HES subtypes.

^bClinical manifestations, comorbidities and cancer diagnoses were assessed between HES diagnosis and EOF (i.e., last physician encounter or death).

^cThe nasal polyps option on the case report form did not specify whether this was chronic rhinosinusitis with nasal polyps or otherwise.

^dOther than asthma and COPD.

^eOther reported comorbidities included allergy (1), angioedema (1), colitis (1), esophagitis (1), eosinophilic gastroenteritis (1), restriction (1) and rhinitis (2).

skin manifestations were common across all (Figure 2). Gastrointestinal involvement was highest in M-HES (34.8%), cardiovascular involvement was highest in L-HES (26.2%) and neuropsychiatric involvement was highest in I-HES (16.8%). The most common distinct clinical manifestations were fatigue (54.2% I-HES, 52.4% L-HES and 42.4% M-HES), skin itch (36.4% M-HES, 35.7% L-HES and 33.5% I-HES) and pain (31.0% L-HES, 30.3% M-HES and 27.1% I-HES; Supplementary Table 2). These clinical manifestations were most commonly of moderate severity in each of the HES subtypes (moderate fatigue: 71.4% M-HES, 63.6% L-HES and 63.1% I-HES; moderate skin itch: 53.3% L-HES, 50.0% M-HES, 42.3% I-HES; and moderate pain: 80.0% M-HES, 73.8% I-HES, 69.2% L-HES; Supplementary Table 3).

The pattern of flare frequency and length, as well as clinical response, differed between subtypes (Table 4). The proportion of patients who experienced ≥ 1 flare/s was highest in the L-HES subtype (33.3%) and lowest in the M-HES subtype (18.2%). However, median flare duration was longest for M-HES (3.8 months) and shortest for I-HES (1.6 months). Clinical response rates were highest for I-HES (75.5%) than other subtypes (63.6%–66.7%) but with longer median time to first response with I-HES (13.9 months) than L-HES (7.2 months) or M-HES (8.2 months). Over 6 years of follow-up, mean FFS was 4.91 years overall, and 5.05, 4.24 and 5.04 years with the M-HES, L-HES and I-HES subtypes, respectively (Supplementary Figure 1). Over the same follow-up period, there were 6 deaths across all subtypes (Supplementary Figure 2).

HES-related hospitalizations were highest for L-HES (45.2%) than other subtypes (25.8%–30.3%) and the mean length of stay was longest with L-HES at 13.6 days, compared with 10.2 and 11.2 days

for I-HES and M-HES, respectively (Supplementary Table 4). Emergency department visits were also most common with L-HES (47.6%) than other subtypes (22.6%–24.2%). The proportions reporting outpatient visits were similar (88%) across subtypes.

3.2 Characteristics and outcomes of patients with HES who received biologics

A total of 123 (43.9%) patients received biologics between HES diagnosis and end of follow-up. These patients had a mean age of 39.2 years at diagnosis, 58.5% were male and median blood eosinophil count was 1,000 cells/ μ l (Table 5). Over half of patients receiving biologics had I-HES (55.3%), while 22.0% had L-HES and 18.7% had M-HES. Asthma (56.9%), nasal polyps (48.8%), anxiety/depression (46.3%), hypertension (35.8%) and vasculitis (23.6%) were the most common comorbidities reported in patients receiving biologics (Table 6).

In total, 41.5% of patients with HES receiving biologics were hospitalized between the index date and end of follow-up, with an average stay of >11 days (Supplementary Table 5). Thirty-nine percent of patients required an emergency department visit and 89.4% attended outpatient visits between the index date and end of follow-up.

Clinical manifestations, OCS use and clinical outcomes were analyzed in the pre-biologic and post-biologic periods among patients who received biologics and who had non-missing dates for ≥ 1 biologics record (*n* = 107). The incidence of fatigue was lower in the 12-month post-biologic period (8.4%) than the pre-biologic period (15.9%), whereas the incidence of gastrointestinal manifestations, itching and pain were slightly higher in the post-biologic period (11.2%, 10.3% and 8.4%, respectively) than in the

TABLE 3 Detailed treatment patterns across HES subtypes.

HES therapies (assessed between diagnosis and EOF)	Overall ^a (N = 280)	Myeloproliferative (N = 66)	Lymphocytic (N = 42)	Idiopathic (N = 155)
Number of distinct HES therapies used, mean (SD) [median]	2.5 (1.5) [2.0]	2.4 (1.7) [2.0]	3.0 (1.7) [3.0]	2.4 (1.3) [2.0]
Time from diagnosis to initiation of therapy (years), mean (SD) [median]	0.7 (1.8) [0.0]	0.4 (1.1) [0.0]	1.0 (2.2) [0.1]	0.6 (1.7) [0.0]
Time from diagnosis to initiation of biologics (years), mean (SD) [median]	3.1 (4.4) [1.8]	2.8 (3.6) [1.9]	2.7 (3.2) [1.6]	3.0 (3.6) [2.0]
HES therapies by treatment category				
Oral corticosteroids, n (%)	250 (89.3)	53 (80.3)	37 (88.1)	143 (92.3)
Patients with a reported maximum daily dose for maintenance therapy, ^b n (%)	190 (76.0)	40 (75.5)	28 (75.7)	112 (78.3)
Maximum daily dose across all oral corticosteroids (mg), mean (SD) [median]	31.7 (19.1) [25.0]	38.6 (19.0) [40.0]	33.6 (16.9) [30.0]	28.4 (19.3) [20.0]
Duration across all oral corticosteroids (months), mean (SD) [median]	23.5 (27.8) [18.3]	22.6 (18.8) [21.1]	15.3 (14.2) [12.7]	28.0 (34.1) [19.8]
Prednisone or prednisolone, n (%)	200 (71.4)	42 (63.6)	27 (64.3)	118 (76.1)
Methylprednisolone, n (%)	46 (16.4)	8 (12.1)	9 (21.4)	23 (14.8)
Cortisone, n (%)	14 (5.0)	6 (9.1)	3 (7.1)	5 (3.2)
Any immunosuppressants or cytotoxic agents, n (%)	178 (63.6)	47 (71.2)	29 (69.0)	93 (60.0)
Imatinib mesylate	57 (20.4)	26 (39.4)	1 (2.4)	27 (17.4)
Azathioprine	40 (14.3)	3 (4.5)	6 (14.3)	29 (18.7)
Methotrexate	29 (10.4)	7 (10.6)	5 (11.9)	13 (8.4)
Hydroxyurea	26 (9.3)	4 (6.1)	6 (14.3)	15 (9.7)
Cyclophosphamide	17 (6.1)	5 (7.6)	5 (11.9)	7 (4.5)
Other ^c	60 (21.4)	18 (27.3)	15 (35.7)	27 (17.4)
Most common biologics, n (%)	123 (43.9)	23 (34.8)	27 (64.3)	68 (43.9)
Mepolizumab	43 (15.4)	11 (16.7)	10 (23.8)	20 (12.9)
Benralizumab	34 (12.1)	4 (6.1)	11 (26.2)	18 (11.6)
Rituximab	34 (12.1)	7 (10.6)	8 (19.0)	16 (10.3)
Alemtuzumab	22 (7.9)	7 (10.6)	4 (9.5)	11 (7.1%)
Dupilumab	22 (7.9)	4 (6.1)	3 (7.1)	15 (9.7)
Other ^d	26 (9.3)	4 (6.1)	8 (19.0)	14 (9.0)

EOF, end of follow-up; HES, hypereosinophilic syndrome; SD, standard deviation.

^aOverall (N = 280) included patients with myeloproliferative (N = 66), lymphocytic (N = 42), idiopathic (N = 155), other (N = 2) and unknown (N = 15) disease subtypes.

^bMaximum daily dose for maintenance therapy values over 60 mg were removed from the summary statistics, as these values likely reflected dosing for burst treatment episodes instead of maintenance therapy.

^cOther immunosuppressants or cytotoxic agents included chlorambucil, cyclosporine, dexamipexole, etoposide, interferon-alpha, pegylated-interferon, ruxolitinib, tofacitinib, vincristine, leflunomide and mycophenolate.

^dOther biologics included omalizumab and reslizumab.

pre-biologic period (7.5%, 6.5% and 2.8%, respectively; Table 7). It should be noted, however, that patient numbers for each of these clinical manifestations were low.

The annualized rate of OCS prescriptions was reduced by 56.8% from 0.44 to 0.19 per person-year and the proportion of patients with ≥ 1 OCS prescription decreased by 64.7% (31.8% pre-biologics and 11.2% post biologics; Table 7). In terms of clinical outcomes, the proportion of patients with ≥ 1 response (complete or partial) was 3.6 times higher in the post-biologics period (23.4%) than in the pre-biologics period (6.5%), while the proportion of patients experiencing ≥ 1 flare was similar in the pre- and post-biologics periods (12.1% and 11.2%, respectively; Table 7).

4 Discussion

This subgroup analysis of real-world European data provides new insights into patient demographics, HES disease characteristics, treatment patterns and outcomes across different

HES subtypes, raising awareness and adding to existing limited data. The analysis also provided real-world data regarding biologic use and treatment outcomes, for which there are limited data. This analysis indicated that patients with I-HES were more treatment responsive compared with patients with L-HES and M-HES, with a greater proportion of patients achieving a clinical response. This is consistent with a previous retrospective chart review study, which indicated that M-HES and L-HES had significantly worse odds of achieving a clinical response with OCS compared with I-HES (odds ratio [95% confidence interval] 0.34 [0.15–0.81], $p = 0.015$ for L-HES and 0.013 [0.0013–0.118, $p = 0.0001$ for M-HES) (13). There are nuances in the data from the current analysis, as the cumulative duration of responses was highest for M-HES, the proportion with complete responses was similar for I-HES and L-HES but lower for M-HES, and time to first response was longer for I-HES than the other subtypes. However, despite these factors, results indicate I-HES may be more treatment responsive than the other subtypes. Additionally, a lower proportion of patients in the current study with I-HES needed hospital or emergency department visits than patients

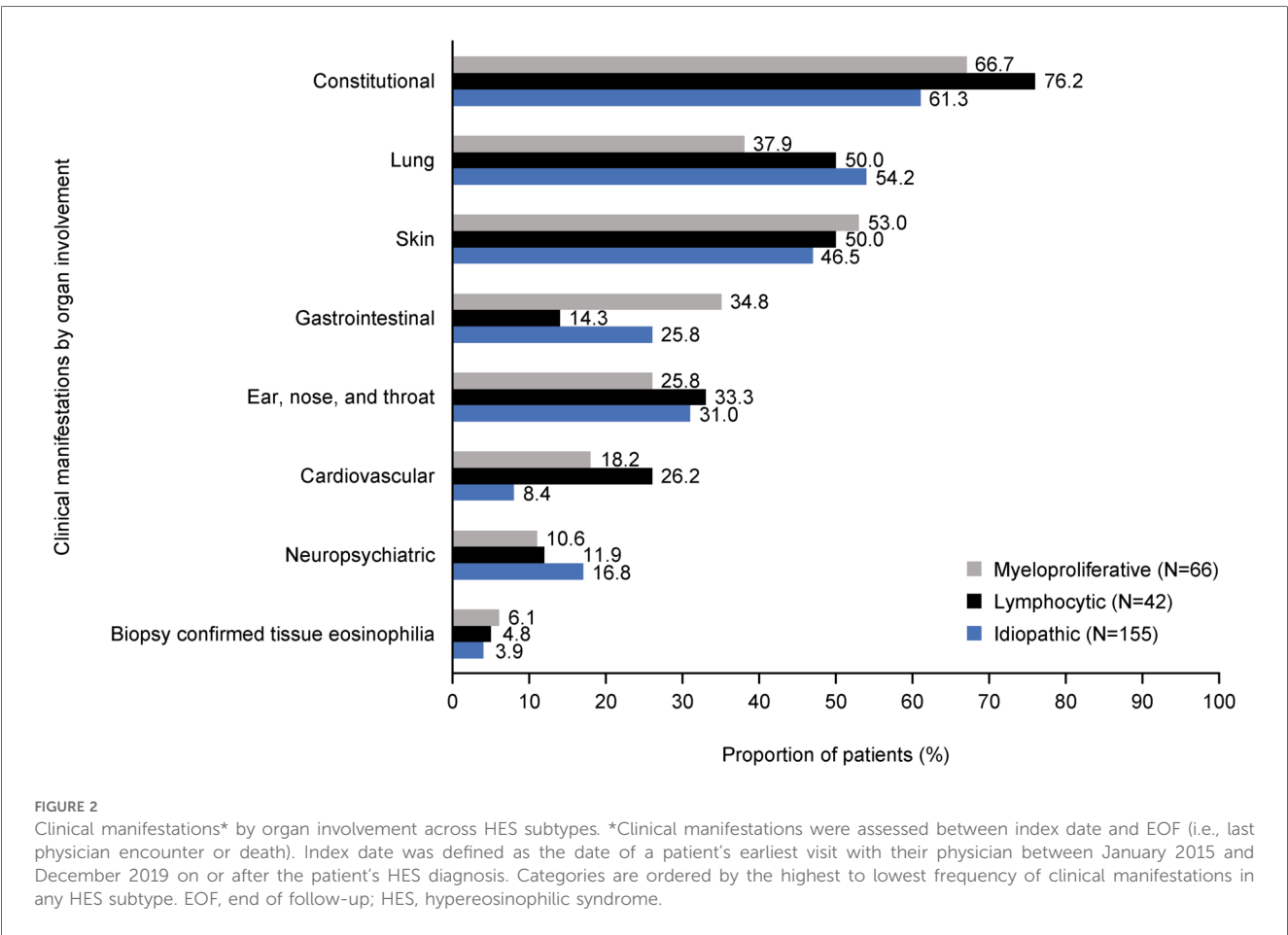
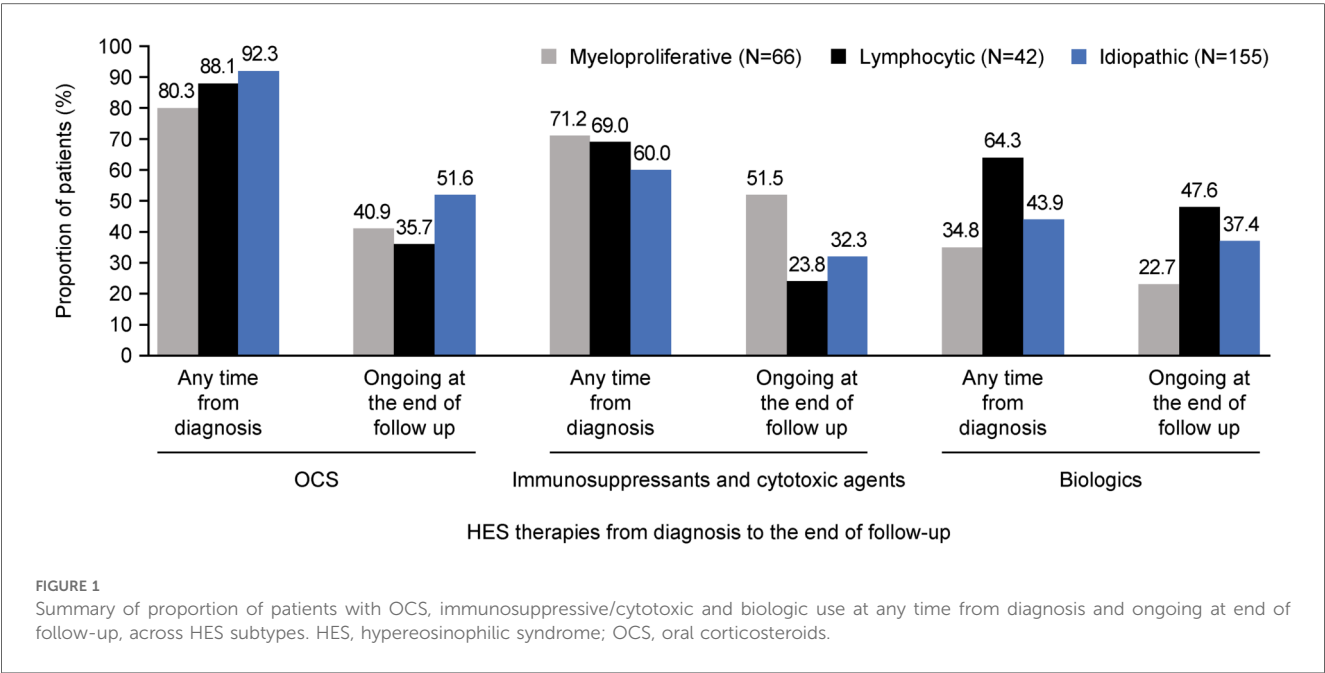


TABLE 4 Clinical outcomes across HES subtypes.

Clinical outcomes	Overall (N = 280)	Myeloproliferative (N = 66)	Lymphocytic (N = 42)	Idiopathic (N = 155)
Flares (between index and EOF) ^a				
Patients who experienced a flare, <i>n</i> (%)	64 (22.9)	12 (18.2)	14 (33.3)	34 (21.9)
Number of flares per year, ^b median (IQR)	0.4 (0.3, 0.7)	0.4 (0.3, 0.7)	0.4 (0.3, 0.6)	0.4 (0.3, 0.7)
Duration of flare(s), cumulative, ^c median (IQR), months	2.1 (0.9, 3.9)	3.8 (1.0, 5.1)	2.2 (1.6, 4.0)	1.6 (0.9, 3.3)
Time to first flare from diagnosis, median (IQR), months	18.4 (10.1, 36.1)	16.8 (10.1, 28.0)	22.7 (9.7, 40.8)	23.0 (11.1, 36.5)
Treatment responses (between diagnosis and EOF) ^d				
Patients who experienced a response, <i>n</i> (%)	200 (71.4)	42 (63.6)	28 (66.7)	117 (75.5)
Duration of response(s), cumulative, ^e median (IQR), months	13.4 (4.8, 24.0)	15.4 (5.5, 25.7)	12.0 (2.9, 22.6)	12.2 (5.1, 25.8)
Time from diagnosis to first response, ^f median (IQR), months	10.8 (4.1, 21.8)	8.2 (3.0, 19.5)	7.2 (3.1, 15.0)	13.9 (4.8, 24.0)
Patients who experienced a complete response, <i>n</i> (%)	113 (40.4)	22 (33.3)	19 (45.2)	68 (43.9)
Patients who experienced a partial response, <i>n</i> (%)	89 (31.8)	20 (30.3)	9 (21.4)	51 (32.9)

EOF, end of follow-up; HES, hypereosinophilic syndrome; IQR, interquartile range.

^aA flare was defined as the worsening of HES-related clinical symptoms or blood eosinophil counts requiring therapy escalation (e.g., increase in current therapy dosage or addition of new therapy).

^bCalculated from patients with ≥ 1 flare.

^cCalculated as the sum of durations for all reported flares.

^dResponses included both complete and partial responses. Complete response: physician-reported improved/resolved symptoms and blood eosinophil counts in the normal range (≤ 500 cells/ μ l). Partial response: physician-reported improved symptoms and blood eosinophil counts, where blood eosinophil count is not yet in the normal range (≤ 500 cells/ μ l) and the patient requires additional therapy. A small number of patients who had >1 different responses reported had both a complete response and a separate response reported.

^eCalculated as the sum of durations of response for all reported responses.

^fAmong patients with ≥ 1 response.

TABLE 5 Demographics and clinical characteristics of patients receiving biologics.

Patient baseline characteristics	Patients receiving biologics (n = 123)
Patient country, <i>n</i> (%)	
France	30 (24.4)
Germany	17 (13.8)
Italy	25 (20.3)
Spain	20 (16.3)
UK	31 (25.2)
Age at HES diagnosis, years, mean (SD)	39.2 (15.6)
Age on index date ^a , years, mean (SD)	41.4 (15.3)
6–11 years, <i>n</i> (%)	4 (3.3)
12–17 years, <i>n</i> (%)	5 (4.1)
Male, <i>n</i> (%)	72 (58.5)
Year of diagnosis, <i>n</i> (%)	
2014 or before	24 (19.5)
2015–2019	99 (80.5)
Disease duration ^b , years, median (IQR)	3.0 (1.8, 5.8)
Length of follow-up ^c , years, median (IQR)	2.5 (1.6, 3.8)
Blood eosinophil count, cells/ μ l, median (IQR) ^d	1,000.0 (450.0, 2,500.0)
Disease subtype, <i>n</i> (%)	
Myeloproliferative	23 (18.7)
Lymphoproliferative	27 (22.0)
Idiopathic	68 (55.3)
Unknown	5 (4.1)

^aIndex date was defined as the date of a patient's earliest visit with their physician between January 2015 and December 2019 on or after the patient's HES diagnosis.

^bDisease duration was calculated as the time between HES diagnosis and EOF (i.e., last physician encounter or death).

^cLength of follow-up was calculated as the time between index date and EOF (i.e., last physician encounter or death).

^dData available for *n* = 106 (86.2%) patients who received biologics. Physicians reported the most recent documented lab test value between the diagnosis date and index date.

TABLE 6 Comorbidities of patients receiving biologics.

Comorbidities, ^a <i>n</i> (%)	Patients receiving biologics (n = 123)
Asthma	70 (56.9)
Nasal polyps	60 (48.8)
Anxiety or depression	57 (46.3)
Hypertension	44 (35.8)
Vasculitis	29 (23.6)
Lower respiratory disease(s) ^b	23 (18.7)
Obesity	18 (14.6)
Diabetes	17 (13.8)
Glomerulonephritis	15 (12.2)
Osteoporosis	14 (11.4)
Liver disease	13 (10.6)
Any cancer	11 (8.9)
Rheumatoid arthritis	6 (4.9)
Cerebrovascular disease	2 (1.6)
Leukemia	2 (1.6)
Other ^c	3 (2.4)

COPD, chronic obstructive pulmonary disease; EOF, end of follow-up; HES, hypereosinophilic syndrome; IQR, interquartile range; SD, standard deviation.

^aComorbidities, and cancer diagnoses were assessed between HES diagnosis and EOF (i.e., last physician encounter or death).

^bOther than asthma and COPD.

^cOther reported comorbidities included allergy (*n* = 1), angioedema (*n* = 1), colitis (*n* = 1), esophagitis (*n* = 1), eosinophilic gastroenteritis (*n* = 1), restriction (*n* = 1) and rhinitis (*n* = 2).

with L-HES and M-HES, suggesting I-HES may be less severe than the other subtypes.

All HES subtypes have a substantial burden of disease, with constitutional; lung; skin; gastrointestinal; ear, nose and throat (ENT); cardiovascular; and neuropsychiatric issues affecting

TABLE 7 Clinical manifestations, OCS reduction and clinical outcomes 12-months pre-/post-biologics.

Clinical manifestations and outcomes	Patients with HES who received biologics (<i>n</i> = 107) ^a	
	≤12 months pre-biologics ^{b,c}	≤12 months post-biologics ^{b,c}
Patients with manifestations, <i>n</i> (%) [95% CI]		
Fatigue	17 (15.9) [9.0, 22.8]	9 (8.4) [3.2, 13.7]
Asthma	11 (10.3) [4.5, 16.0]	12 (11.2) [5.2, 17.2]
Gastrointestinal ^d	8 (7.5) [2.5, 12.5]	12 (11.2) [5.2, 17.2]
Itch	7 (6.5) [1.9, 11.2]	11 (10.3) [4.5, 16.0]
Shortness of breath	5 (4.7) [0.7, 8.7]	5 (4.7) [0.7, 8.7]
Cardiovascular ^e	4 (3.7) [0.1, 7.3]	6 (5.6) [1.2, 10.0]
Pain	3 (2.8) [0, 5.9]	9 (8.4) [3.2, 13.7]
Rash	2 (1.9) [0, 4.4]	4 (3.7) [0.1, 7.3]
OCS use		
Annualized rate of OCS prescription, ^f PPY	0.44	0.19
Patients with ≥1 OCS prescriptions, ^f <i>n</i> (%) [95% CI]	34 (31.8) [23.0, 40.6]	12 (11.2) [5.2, 17.2]
Clinical outcomes, <i>n</i> (%) [95% CI]		
Patients with ≥1 response, ^g	7 (6.5) [1.9, 11.2]	25 (23.4) [15.3, 31.4]
Patients with ≥1 flare, ^h	13 (12.1) [6.0, 18.3]	12 (11.2) [5.2, 17.2]

CI, confidence interval; EOF, end of follow-up; HES, hypereosinophilic syndrome; OCS, oral corticosteroid; PPY, per person-year.

^a123 out of 280 patients received biologics between HES diagnosis and EOF. 107 out of those 123 patients had non-missing dates for ≥1 biologics record. This analysis is out of those 107 patients.

^bThe pre-biologics period was defined as 12 months before or on the initiation of biologics. The post-biologics period was defined as 12 months after the initiation of biologics.

^cFor the pre-biologics period, only OCS prescriptions and person-years after HES diagnosis were included. For the post-biologics period, patients were censored if they died or had <12 months of follow-up period after biologics initiation.

^dIncludes diarrhea, abdominal pain, nausea/vomiting, difficulty in swallowing food.

^eIncludes cardiomyopathy, heart failure, thromboembolism, ischemic heart disease, valvular disease and arterial hypertension.

^fOCS prescriptions between HES diagnosis and EOF (i.e., last physician or death) were assessed.

^gResponses included both complete and partial responses. A complete response was defined as having physician-reported improved or resolved symptoms and normal blood eosinophil counts ($<0.5 \times 10^9/L$). A partial response was defined as having physician-reported improved symptoms and blood eosinophil counts, where blood eosinophil counts is not yet in the normal range and the patient still requires additional therapy. Responses were assessed between HES diagnosis date and EOF (i.e., last physician encounter or death). A small share of patients who had >1 different responses reported had both a complete response and a separate response reported.

^hA flare was defined as the worsening of HES-related clinical symptoms or blood eosinophil counts requiring therapy escalation (e.g., increase in the dose of the current therapy or addition of new therapy). Flares were assessed between index date and EOF (i.e., last physician encounter or death). Index date was defined as the date of a patient's earliest visit with their physician between January 2015 and December 2019 on or after the patient's HES diagnosis.

8.4%–76.2% of patients in this study. This is consistent with a previous retrospective study of 188 patients with HES, which identified skin, pulmonary and gastrointestinal adverse impacts as being the most common clinical manifestations (28). The current analysis identified cardiovascular manifestations in 8% of patients with I-HES and up to 26% in those with L-HES; this is consistent with a case study review, which reported cardiac, rather than cardiovascular, manifestations in 12.9% of patients with L-HES, 14.9% with M-HES and 22.4% with I-HES (9).

There were also differences between HES subtypes in the prevalence of clinical manifestations within the organ domains of

constitutional, cardiovascular, gastrointestinal and lung in this study. A higher proportion of patients with L-HES experienced constitutional manifestations such as pain, ENT manifestations such as sinus headache/facial pain/pressure and cardiovascular manifestations such as heart failure and thromboembolism, than with the other subtypes. Patients with M-HES experienced skin manifestations such as rash and gastrointestinal manifestations such as diarrhea, abdominal pain and nausea/vomiting slightly more frequently than patients with other subtypes. While overall, M-HES was the subtype with the highest prevalence of skin manifestations, the prevalence of hives/urticaria was highest in patients with L-HES. This corresponds with a case review study based on data from the French Reference Center for Hypereosinophilic Syndromes (CEREO), which reported eczema-like lesions, angioedema and urticaria in over 26% of patients with L-HES (24). However, while our data suggested that around half of patients with L-HES had skin manifestations, a retrospective study of 21 patients with L-HES initiated by the French Eosinophil Network, reported that 81% had skin manifestations (23). Finally, patients with I-HES had the highest prevalence of lung manifestations such as asthma and dyspnea and neuropsychiatric manifestations, such as sensory neuropathy, than the other subtypes.

Along with clinical manifestations, the high dosage of OCS received by patients in this study also underscores the substantial disease burden (mean maximum daily dose across all patients was 31.7 mg). The use of OCS, immunosuppressant/cytotoxic agents and biologics differed between HES subtypes. At baseline, the proportion receiving OCS was highest in patients with I-HES, the proportion receiving immunosuppressants/cytotoxic agents was highest in patients with M-HES and biologics were used by more patients with L-HES than the other subtypes. This is in accordance with findings from a previous review article that included individual case and aggregated data (9). This treatment pattern was seen with ongoing treatments at end of follow-up, with OCS being most used in I-HES, immunosuppressants/cytotoxic agents in M-HES and biologics in L-HES, with each prevalent drug class being used by approximately half of patients in their respective subtype.

Compared with the pre-biologic period, following post-biologic initiation there was a 56.8% reduction in the annualized rate of OCS prescriptions and a 64.7% decrease in the proportion of patients with ≥1 OCS prescription. Clinical response to treatment was also improved; 3.6 times as many patients had ≥1 clinical response in the ≤12-month post-biologic period, compared with pre-biologic. These findings are consistent with randomized controlled trials and open-label extensions that support the OCS-sparing effect, efficacy and safety of mepolizumab and benralizumab in the treatment of HES (18–20, 29, 30). The proportion of patients experiencing ≥1 flare was similar in the pre- and post-biologics periods, which may have reflected the fact that the study did not differentiate between different types of biologics used, including anti-IL-5, anti-IL-5 receptor, anti-cluster of differentiation (CD)20, anti-CD52, anti-IL-4 and anti-IL-13 therapies. A range of studies, however, have demonstrated that biologics targeting IL-5 or the IL-5 receptor can significantly reduce flares in HES (18, 25, 26, 31, 32).

Additionally, there are clear knowledge gaps in terms of the efficacy of biologic therapies targeting eosinophilic inflammation in different HES subtypes (15). Therefore, examining the impact of different biologics on clinical outcomes in each HES subtypes, including those targeting IL-5/IL-5 receptor, would be an interesting topic to explore in future studies.

A strength of this study is the real-world nature of the data, which were collected across five European countries, meaning the findings may be generalizable across these healthcare systems and potentially more widely. Limitations of the study include that these were descriptive *post hoc* analyses with no statistical comparisons made, and there was no control population for the characterization of the biologics group. Therefore, the results should be seen as providing preliminary insights with the goal of providing hypotheses for further investigations.

5 Conclusion

Different HES subtypes are associated with differing disease burdens, treatment patterns and clinical outcomes. Biologic use appeared to be associated with numerically reduced OCS use and improved clinical responses, although these findings were not stratified by HES subtype. To improve patient care, further research is needed to optimize awareness regarding the differing clinical needs associated with each HES subtype and further characterize the impact of different biologic treatment across different subtypes.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

Ethics statement

The study was submitted to the Western Copernicus Group Institutional Review Board and was granted exemption status with a waiver of authorization issued (December 23, 2020; #1-1383121-1), in accordance with the local legislation and institutional requirements. Only anonymized data were collected and the reported data reflect aggregate analyses without patient identification. Written informed consent to participate in this study was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and the institutional requirements.

Author contributions

JH: Conceptualization, Writing – review & editing, Visualization, Writing – original draft. LH: Conceptualization, Data curation, Investigation, Formal analysis, Writing – original draft, Visualization, Writing – review & editing. WdCJ: Writing – review

& editing, Writing – original draft, Formal analysis, Visualization. MER: Visualization, Writing – original draft, Writing – review & editing. MSD: Writing – review & editing, Writing – original draft, Formal analysis, Conceptualization, Visualization, Data curation, Investigation. RA-C: Writing – review & editing, Conceptualization, Writing – original draft, Visualization.

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Conflict of interest

JH and RA-C are employed by GSK and hold financial equities in GSK. LH, WdCJ and MSD are employees of the Analysis Group, Inc.; Analysis Group, Inc. received payment from GSK to conduct the study. MER is a consultant for Pulm One, Spoon Guru, ClostraBio, Serpin Pharm, Allakos, Celldex, Uniquitybio, Santa Ana Bio, EnZen Therapeutics, Bristol Myers Squibb, AstraZeneca, Pfizer, GSK, Regeneron/Sanofi, Revolo Biotherapeutics and Guidepoint, and has an equity interest in the first nine listed and royalties from reslizumab (Teva Pharmaceuticals), PEESV2 (Mapi Research Trust) and UpToDate. MER is an inventor of patents owned by Cincinnati Children's Hospital.

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References

- Shomali W, Gotlib J. World health organization-defined eosinophilic disorders: 2022 update on diagnosis, risk stratification, and management. *Am J Hematol*. (2022) 97:129–48. doi: 10.1002/ajh.26352
- Leru PM. Eosinophilic disorders: evaluation of current classification and diagnostic criteria, proposal of a practical diagnostic algorithm. *Clin Transl Allergy*. (2019) 9:36. doi: 10.1186/s13601-019-0277-4
- Valent P, Klion AD, Roufosse F, Simon D, Metzgeroth G, Leiferman KM, et al. Proposed refined diagnostic criteria and classification of eosinophil disorders and related syndromes. *Allergy*. (2023) 78:47–59. doi: 10.1111/all.15544
- Orphanet Report Series. *Prevalence of rare diseases: Bibliographic data*. (2022). Available at: https://www.orpha.net/orphacom/cahiers/docs/GB/Prevalence_of_rare_diseases_by_alphabetical_list.pdf (Accessed January 18, 2022).
- Crane MM, Chang CM, Kobayashi MG, Weller PF. Incidence of myeloproliferative hypereosinophilic syndrome in the United States and an estimate of all hypereosinophilic syndrome incidence. *J Allergy Clin Immunol*. (2010) 126:179–81. doi: 10.1016/j.jaci.2010.03.035
- Requena G, Logie J, Gibbons DC, Steinfeld J, Van Dyke MK. The increasing incidence and prevalence of hypereosinophilic syndrome in the United Kingdom. *Immun Inflamm Dis*. (2021) 9:1447–51. doi: 10.1002/iid3.495
- Curtis C, Ogbogu P. Hypereosinophilic syndrome. *Clin Rev Allergy Immunol*. (2016) 50:240–51. doi: 10.1007/s12016-015-8506-7
- Kahn JE, Groh M, Lefevre G. (A critical appraisal of) classification of hypereosinophilic disorders. *Front Med (Lausanne)*. (2017) 4:216. doi: 10.3389/fmed.2017.00216
- Requena G, van den Bosch J, Akuthota P, Kovalski A, Steinfeld J, Kwon N, et al. Clinical profile and treatment in hypereosinophilic syndrome variants: a pragmatic review. *J Allergy Clin Immunol Pract*. (2022) 10:2125–34. doi: 10.1016/j.jaip.2022.03.034
- Shomali W, Gotlib J. World health organization and international consensus classification of eosinophilic disorders: 2024 update on diagnosis, risk stratification, and management. *Am J Hematol*. (2024) 99:946–68. doi: 10.1002/ajh.27287
- Roufosse F. Management of hypereosinophilic syndromes. *Immunol Allergy Clin North Am*. (2015) 35:561–75. doi: 10.1016/j.iac.2015.05.006
- Klion AD. How I treat hypereosinophilic syndromes. *Blood*. (2015) 126:1069–77. doi: 10.1182/blood-2014-11-551614
- Khoury P, Abiodun AO, Holland-Thomas N, Fay MP, Klion AD. Hypereosinophilic syndrome subtype predicts responsiveness to glucocorticoids. *J Allergy Clin Immunol Pract*. (2018) 6:190–5. doi: 10.1016/j.jaip.2017.06.006
- Dispenza MC, Bochner BS. Diagnosis and novel approaches to the treatment of hypereosinophilic syndromes. *Curr Hematol Malig Rep*. (2018) 13:191–201. doi: 10.1007/s11899-018-0448-8
- Kuang FL, Khoury P, Weller PF, Wechsler ME, Klion AD. Biologics and hypereosinophilic syndromes: knowledge gaps and controversies. *J Allergy Clin Immunol Pract*. (2023) 11:2666–71. doi: 10.1016/j.jaip.2023.07.026
- EMA. Mepolizumab (Nucala) summary of product characteristics. European Medicines Agency (2022). Available at: https://www.ema.europa.eu/en/documents/product-information/nucala-epar-product-information_en.pdf (Accessed January 18, 2024).
- Food and Drug Administration (FDA). Mepolizumab (Nucala) prescribing information. Food and Drug Administration (2023). Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/125526Orig1s021,761122Orig1s011Corrected_lbl.pdf (Accessed June 12, 2024).
- Roufosse F, Kahn JE, Rothenberg ME, Wardlaw AJ, Klion AD, Kirby SY, et al. Efficacy and safety of mepolizumab in hypereosinophilic syndrome: a phase iii, randomized, placebo-controlled trial. *J Allergy Clin Immunol*. (2020) 146:1397–405. doi: 10.1016/j.jaci.2020.08.037
- Gleich GJ, Roufosse F, Chupp G, Faguer S, Walz B, Reiter A, et al. Safety and efficacy of mepolizumab in hypereosinophilic syndrome: an open-label extension study. *J Allergy Clin Immunol Pract*. (2021) 9:4431–40.e1. doi: 10.1016/j.jaip.2021.07.050
- Kuang FL, Legrand F, Makiya M, Ware J, Wetzler L, Brown T, et al. Benralizumab for pdgfra-negative hypereosinophilic syndrome. *N Engl J Med*. (2019) 380:1336–46. doi: 10.1056/NEJMoa1812185
- Kuang FL, Klion AD. Biologic agents for the treatment of hypereosinophilic syndromes. *J Allergy Clin Immunol Pract*. (2017) 5:1502–9. doi: 10.1016/j.jaip.2017.08.001
- Hwee J, Huynh L, Du S, Kwon N, Jakes RW, Alfonso-Cristancho R, et al. Hypereosinophilic syndrome in Europe: retrospective study of treatment patterns, clinical manifestations, and healthcare resource utilization. *Ann Allergy Asthma Immunol*. (2023) 130:768–75. doi: 10.1016/j.anaai.2023.02.022
- Lefevre G, Copin MC, Staumont-Salle D, Avenel-Audran M, Aubert H, Taieb A, et al. The lymphoid variant of hypereosinophilic syndrome: study of 21 patients with Cd3-Cd4+ aberrant T-cell phenotype. *Medicine (Baltimore)*. (2014) 93:255–66. doi: 10.1097/MD.0000000000000088
- Laurent C, Lefevre G, Kahn JE, Staumont-Salle D, Felten R, Puget M, et al. Cutaneous manifestations of lymphoid-variant hypereosinophilic syndrome. *Br J Dermatol*. (2022) 187:1011–3. doi: 10.1111/bjd.21782
- Pane F, Lefevre G, Kwon N, Bentley JH, Yancey SW, Steinfeld J. Characterization of disease flares and impact of mepolizumab in patients with hypereosinophilic syndrome. *Front Immunol*. (2022) 13:935996. doi: 10.3389/fimmu.2022.935996
- Rothenberg ME, Roufosse F, Faguer S, Gleich GJ, Steinfeld J, Yancey SW, et al. Mepolizumab reduces hypereosinophilic syndrome flares irrespective of blood eosinophil count and interleukin-5. *J Allergy Clin Immunol Pract*. (2022) 10:2367–74.e3. doi: 10.1016/j.jaip.2022.04.037
- Kuang FL. Approach to patients with eosinophilia. *Med Clin North Am*. (2020) 104:1–14. doi: 10.1016/j.mcna.2019.08.005
- Ogbogu PU, Bochner BS, Butterfield JH, Gleich GJ, Huss-Marp J, Kahn JE, et al. Hypereosinophilic syndrome: a multicenter, retrospective analysis of clinical characteristics and response to therapy. *J Allergy Clin Immunol*. (2009) 124:1319–25.e3. doi: 10.1016/j.jaci.2009.09.022
- Rothenberg ME, Klion AD, Roufosse FE, Kahn JE, Weller PF, Simon HU, et al. Treatment of patients with the hypereosinophilic syndrome with mepolizumab. *N Engl J Med*. (2008) 358:1215–28. doi: 10.1056/NEJMoa070812
- Roufosse FE, Kahn JE, Gleich GJ, Schwartz LB, Singh AD, Rosenwasser LJ, et al. Long-term safety of mepolizumab for the treatment of hypereosinophilic syndromes. *J Allergy Clin Immunol*. (2013) 131:461–7.e1–5. doi: 10.1016/j.jaci.2012.07.055
- Reiter A, Lefevre G, Cid MC, Kwon N, Mavropoulou E, Yancey SW, et al. Association between baseline therapy and flare reduction in mepolizumab-treated patients with hypereosinophilic syndrome. *Front Immunol*. (2022) 13:840974. doi: 10.3389/fimmu.2022.840974
- Kuang FL, Fay MP, Ware J, Wetzler L, Holland-Thomas N, Brown T, et al. Long-term clinical outcomes of high-dose mepolizumab treatment for hypereosinophilic syndrome. *J Allergy Clin Immunol Pract*. (2018) 6:1518–27.e5. doi: 10.1016/j.jaip.2018.04.033

Supplementary material

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/falgy.2025.1605397/full#supplementary-material>