Original Article

An International, Retrospective Study of Off-Label Biologic Use in the Treatment of Hypereosinophilic Syndromes

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What is already known about this topic? Hypereosinophilic syndrome (HES) is a group of rare diseases with few treatment options.

What does this article add to our knowledge? It provides retrospective data on the efficacy and safety of biologics for the treatment of HES.

How does this study impact current management guidelines? Biologics may offer a safe alternative treatment for HES and the clinical response may vary by HES subtype.

BACKGROUND: Treatment of hypereosinophilic syndrome (HES) often requires the use of immunomodulators with substantial side effect profiles. The emergence of biologics offers an alternative treatment modality.

OBJECTIVE: To examine real-world practice data to describe the safety and consequences of various biologics suspected to directly or indirectly affect eosinophilic inflammation for the treatment of HES.

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Abbreviations used
ACR- American College of Rheumatology
AEC- Absolute eosinophil count
EGPA- Eosinophilic granulomatosis with polyangiitis
FDA- US Food and Drug Administration
HES- Hypereosinophilic syndrome
IHES- Idiopathic hypereosinophilic syndrome
LHES- Lymphoid hypereosinophilic syndrome
MHES- Myeloid hypereosinophilic syndrome

METHODS: Retrospective data from 13 centers were collected via an online Research Electronic Data Capture repository. Inclusion criteria included (1) peripheral eosinophil count of 1,500/mm^3 or greater without a secondary cause; (2) clinical manifestations attributable to the eosinophilia; and (3) having received mepolizumab (anti-IL-5), benralizumab (afucosylated anti-IL-5 receptor α), omalizumab (anti-IgE), alemtuzumab (anti-CD52), dupilumab (anti-IL-4 receptor α), or reslizumab (anti-IL-5) outside a placebo-controlled clinical trial.
RESULTS: Of the 151 courses of biologics prescribed for 121 patients with HES, 59% resulted in improved HES symptoms and 77% enabled tapering of other HES medications. Overall, 105 patients were receiving daily systemic glucocorticoids at the time of a biologic initiation and were able to reduce the glucocorticoid dose by a median reduction of 10 mg of daily prednisone equivalents. Biologics were generally safe and well-tolerated other than infusion reactions with alemtuzumab. Thirteen of 24 patients had clinical improvement after switching biologics and nine patients responded to increasing the dose of mepolizumab after a lack of response to a lower dose.
CONCLUSIONS: Biologics may offer a safer treatment alternative to existing therapies for HES, although the optimal dosing and choice for each subtype of HES remain to be determined. Limitations of this study include its retrospective nature and intersite differences in data collection and availability of each biologic. © **2022 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2022;■:■-■)**

Key words: *Hypereosinophilic syndrome; Eosinophil; Eosinophilic granulomatosis with polyangiitis; Biologic*

INTRODUCTION

Hypereosinophilic syndrome (HES) is a rare group of heterogeneous disease sharing the common features of a sustained peripheral blood eosinophil count of 1,500 cells/mm^3 or greater in the absence of a secondary cause, with clinical manifestations attributable to the eosinophilia.[1] Multiple subtypes of HES exist, reflecting various mechanisms of underlying pathophysiology.[2] Myeloid HES (MHES) is associated with definite or presumed molecular abnormalities, such as the deletion creating *FIP1L1*—platelet-derived growth factor receptor A fusion on chromosome 4, which drive myeloid proliferation. In lymphoid HES (LHES), eosinophils expand in response to eosinophilopoietic cytokine(s) produced by a clonal and/or aberrant T-cell population. Overlap HES includes conditions with single organ involvement (eosinophilic gastrointestinal disease, eosinophilic pneumonia, atopic dermatitis, and atopic asthma) and clinically distinct eosinophilic disorders that overlap in clinical presentation with other types of HES, such as HES that meets American College of Rheumatology (ACR) criteria for eosinophilic granulomatosis with polyangiitis (EGPA) without definitive evidence of vasculitis (EGPA overlap). Hypereosinophilic disorders that do not fit one of the defined subtypes are categorized as idiopathic HES (IHES). With the exception of imatinib, which approaches 100% efficacy for platelet-derived growth factor receptor—associated MHES but has little to no efficacy in nonmyeloid forms of HES, targeted treatment options remain limited and management hinges on the off-label use of immunosuppressants, mainly systemic glucocorticoids alone or in conjunction with glucocorticoid-sparing agents that are often poorly tolerated or ineffective.[3] Biologics that reduce eosinophilic inflammation directly or indirectly offer a possible alternative treatment modality. Although mepolizumab is currently the only US Food and Drug Administration (FDA)-approved biologic for the treatment of HES, a number of additional biologics that affect eosinophilic inflammation are used through compassionate use protocols or off-label for other comorbid allergic indications. The goal of this study was to examine real-world practice data in a retrospective manner to study the use of various biologics for the treatment of HES.

METHODS

Patient identification

The need for multicenter collaboration to formulate approaches to HES treatment was first identified at the premeeting workshop of the July 2019 biannual meeting of the International Eosinophil Society.[4] Subsequently, patients meeting criteria for HES, who were evaluated before December 2020 at 13 participating institutions (10 in the United States, two in Europe, and one in Israel) with expertise in eosinophilic disorders, were included in the study. Patients were identified by a search of medical records or from an existing database of HES patients (see Table E1 in this article's Online Repository at www.jaci-inpractice.org). Inclusion criteria were (1) a blood absolute eosinophil count (AEC) of 1,500 cells/mm^3 or greater (two values confirmed at least 1 month apart) without a secondary cause (such as helminth infection, drug hypersensitivity, immunodeficiency, or malignancies); (2) clinical manifestations attributable to the eosinophilia; and (3) having received mepolizumab, benralizumab, omalizumab, alemtuzumab, dupilumab, or reslizumab outside a placebo-controlled trial. After data entry, HES subtypes were assigned based on the following criteria: (1) HES patients with an abnormal clonal T-cell population identified by flow cytometry and known to produce IL-5 were labeled as LHES; (2) overlap HES included those with single organ involvement; (3) patients categorized as having EGPA met at least four of six criteria for EGPA as described by the ACR[5]; (4) a diagnosis of MHES required the detection of a molecular genetic alteration known to be associated with eosinophilic myeloid neoplasms; and (5) all others were categorized as having IHES.

Data collection

Study data were collected and managed using Research Electronic Data Capture tools.[6,7] Research Electronic Data Capture is a secure Web-based software platform designed to support data capture for research studies. It provides (1) an intuitive interface for validated data capture; (2) audit trails to track data manipulation and export procedures; (3) automated export procedures for seamless data downloads to common statistical packages; and (4) procedures for data integration and interoperability with external sources. Potential patients for data entry were identified from in-house research databases and/or

TABLE I. Patient characteristics by participating site

Site	Patients, n	Sex (M/F)	Medican age at first biologic, (range)	Geometric mean peak eosinophil count, cell/mm^3 (range)	HES subtype, (n)	Biologic given, n					
						A	B	D	M	O	R
Beth Israel	7	4/3	58 (20-79)	8,420 (3,330-19,540)	IHES (5) LHES (2)				7		*
Cincinnati Children's	8	5/3	17 (10-21)	4,525 (1,510-33,730)	IHES (6) EGPA Overlap (1) Other overlap (1)		2	3	4	2	
Wolfson-Israel	4	2/2	65 (57-77)	8,188 (4,190-16,000)	IHES (2) EGPA Overlap (2)				3		3
Mayo Clinic	8	4/4	43 (25-67)	8,362 (4,000-29,394)	IHES (8)				8		
MD Anderson	9	5/4	49 (19-82)	7,593 (2,100-40,000)	IHES (7) LHES (2)	7			2	1	
National Jewish Health	5	1/4	68 (59-86)	3,536 (2,200-4,900)	IHES (3) EGPA Overlap (1) Other overlap (1)		2		4		
National Institutes of Health	37	17/20	42 (13-68)	7,430 (1,700-89,000)	IHES (11) LHES (3) MHES (1) EGPA Overlap (22)	1	6	2	36	7	2
Northwestern University	13	3/10	44 (24-60)	7,806 (2,700-16,500)	IHES (4) LHES (3) EGPA Overlap (4) Other overlap (2)		3	1	13	1	
Ohio State University	3	1/2	45 (36-47)	2,392 (1,960-2,920)	IHES (1) EGPA Overlap (1) Other overlap (1)			1	2		
Université Libre Bruxelles	23	11/12	50 (18-64)	7,731 (2,170-53,031)	IHES (8) LHES (6) EGPA Overlap (9)		2	1	21		
University of Bern	1	0/1	69	8,760	IHES (1)				1		
University of California-San Diego	1	1/0	85	7,300	Other overlap (1)			1			
University of Wisconsin-Madison	2	0/2	26 (22-29)	9,500 (8,900-10,140)	IHES (2)				2		
Total	121	54/67	45 (10-86)	7,311 (1,510- 89,000)	IHES (58) LHES (16) MHES (1) EGPA Overlap (40) Other overlap (6)	8	15	9	103	11	5

A, alemtuzumab; *B*, benralizumab; *D*, dupilumab; *EGPA*, eosinophilic granulomatosis with polyangiitis; *HES*, hypereosinophilic syndrome; *IHES*, idiopathic hypereosinophilic syndrome; *LHES*, lymphoid hypereosinophilic syndrome; *M*, mepolizumab; *MHES*, myeloid hypereosinophilic syndrome; *O*, omalizumab; *R*, reslizumab.
*Drug not available at this site.

electronic medical record searches, depending on the site (see Figure E1 in this article's Online Repository at www.jaci-inpractice.org). Clinical and laboratory data were collected via chart review and entered without identifiers, in accordance with local institutional review boards (Figure E1). No duplicates were identified based on the date of birth, sex, or clinical characteristics. Hematologic response to a biologic was defined as a reduction in peripheral blood AEC to less than 1,000 cells/mm^3. Clinical response was defined as an improvement in HES manifestations or the ability to taper other HES medications without the worsening of symptoms.

Symptom assessment

Eosinophil-mediated symptoms and findings were reported in a binary manner as present or absent and grouped by organ system involvement. Analysis was limited to those for whom data were entered for the respective symptom or finding.

Statistical analysis

The percent reduction in daily prednisone equivalents was calculated as the difference in pretreatment and posttreatment prednisone divided by pretreatment prednisone requirements.

RESULTS

Patient characteristics

Of the 121 patients enrolled (range, 1-37 subjects/site at 13 different sites), 54 were male (45%) (Table I). Median age at initiation of first biologic was 45 years (range, 10-86 years). Peak recorded peripheral blood AEC was 1,510 to 89,000 cells/mm^3 (mean, 7,311 cells/mm^3). Flow cytometry identified an abnormal T-cell immunophenotype in 16 patients, who were therefore categorized as having LHES. Consistent with prior reports, the most common abnormal T-cell immunophenotype was CD3$^-$CD4$^+$, found in 11 patients. The presence of CD3$^+$CD4$^-$

TABLE II. Patient characteristics by biologic administered

Patient characteristic	Alemtuzumab (8)	Benralizumab (15)	Dupilumab (9)	Mepolizumab (103)	Omalizumab (11)	Reslizumab (5)	Any biologic*
Median age at biologic initiation, (range)	53 (33-82)	48 (15-69)	42 (11-85)	45 (13-86)	38 (10-62)	67 (41-77)	45 (10-86)
Female sex (%)	50	60	67	53	64	40	55
Race (%)							
Asian	—	—	—	6	—	—	4
Black	13	7	—	3	—	—	4
Unknown	13	13	11	8	9	—	9
White	75	80	89	84	91	100	85
Ethnicity (%)							
Non-Hispanic	75	87	89	87	91	100	87
Hispanic	25	7	11	5	9	—	7
Unknown	—	7	—	8	—	—	6
Peak absolute eosinophil count, cells/mm^3, mean (range)	7,923 (2,140-23,530)	7,508 (1,510-43,700)	4,943 (1,960-14,040)	7,641 (1,700-89,000)	4,253 (1,510-35,000)	4,821 (2,600-16,000)	7,311 (1,510-89,000)
HES subtype (% [n])							
Idiopathic HES	63 (5)	27 (4)	67 (6)	46 (48)	55 (6)	80 (4)	48 (73)
Lymphoid HES	37 (3)	13 (2)	22 (2)	15 (15)	9 (1)	—	15 (23)
Myeloid HES	—	—	—	1 (1)	—	—	1 (1)
Eosinophilic granulomatosis with polyangiitis Overlap	—	40 (6)	—	34 (35)	36 (4)	20 (1)	31 (46)
Other overlap	—	20 (3)	11 (1)	4 (4)	—	—	5 (8)

HES, hypereosinophilic syndrome.
Lymphoid HES is an abnormal clonal T-cell population identified by flow cytometry. Myeloid HES requires the detection of a mutation associated with eosinophilic myeloid neoplasms.
*Data in this column are taken from the first initiation of a biologic.

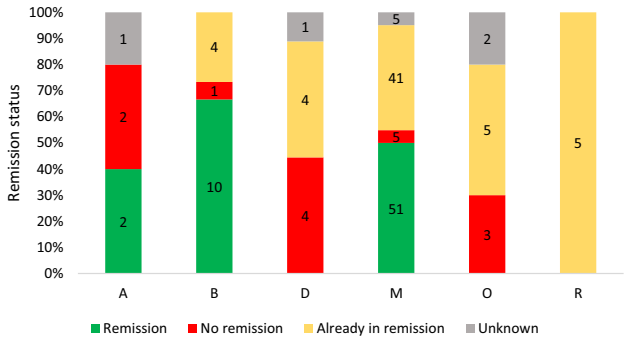

FIGURE 1. Hematologic remission (defined as absolute eosinophil count <1,000 cells/mm^3) status by biologic administered. *A*, alemtuzumab; *B*, benralizumab; *D*, dupilumab; *M*, mepolizumab; *O*, omalizumab; *R*, reslizumab.

$CD8^-$, $CD3^+CD4^+CD8^+$, or $CD3^+CD4^+CD25^+$ T cells in the peripheral blood was documented in one patient each and was confirmed to have a clonal T cell receptor rearrangement by polymerase chain reaction. The remaining two LHES patients were reported to have $CD52^+CD117^+$ and $CD3^+CD5^+CD7^+CD2^+CD25^+$ T-cell immunophenotypes. Among the 95 patients who were evaluated for molecular abnormalities associated with eosinophilic myeloid neoplasms, one was positive for JAK2 V617F and was classified as having MHES. The overlap HES subgroup was composed of 46 patients, 40 of whom met ACR criteria for EGPA and six of whom had single-organ eosinophilic involvement (three gastrointestinal, two dermatologic, and one pulmonary). The remaining 58 patients were categorized as having IHES. Overall, in 85 HES patients pulmonary manifestations were most common, followed by dermatologic (n = 70), gastrointestinal (n = 50), and neurologic (n = 34). Only 10 patients had cardiac manifestations. All 16 LHES patients had dermatologic manifestations.

Biologics prescribed

A total of 151 courses of biologics for HES treatment were received by the 121 patients studied (Tables I and II). Patient characteristics were largely similar across biologics, including age at biologic initiation, race, ethnicity, and peak AEC. Mepolizumab was the most common biologic received (103 of 151 courses; 68%). Among the diagnoses for which biologics were administered, IHES and EGPA were the most common (48% and 33%, respectively).

Prescribing patterns

A total of 151 courses of biologics were received outside a placebo-controlled trial, 30 of which were received as an open-label extension after the completion of a placebo-controlled trial. Three were initially received in an open-label trial, 18 through compassionate use or expanded access programs, and 95 by provider prescription. For five patients, the context of the biologic course was not reported (data not shown). Of the 33 patients in an open label trial or extension, 31 continued to receive the same biologic (eight remained in the trial, 20 in expanded access, and three by provider prescription) and two changed to a different biologic. Mepolizumab (97 of 103),

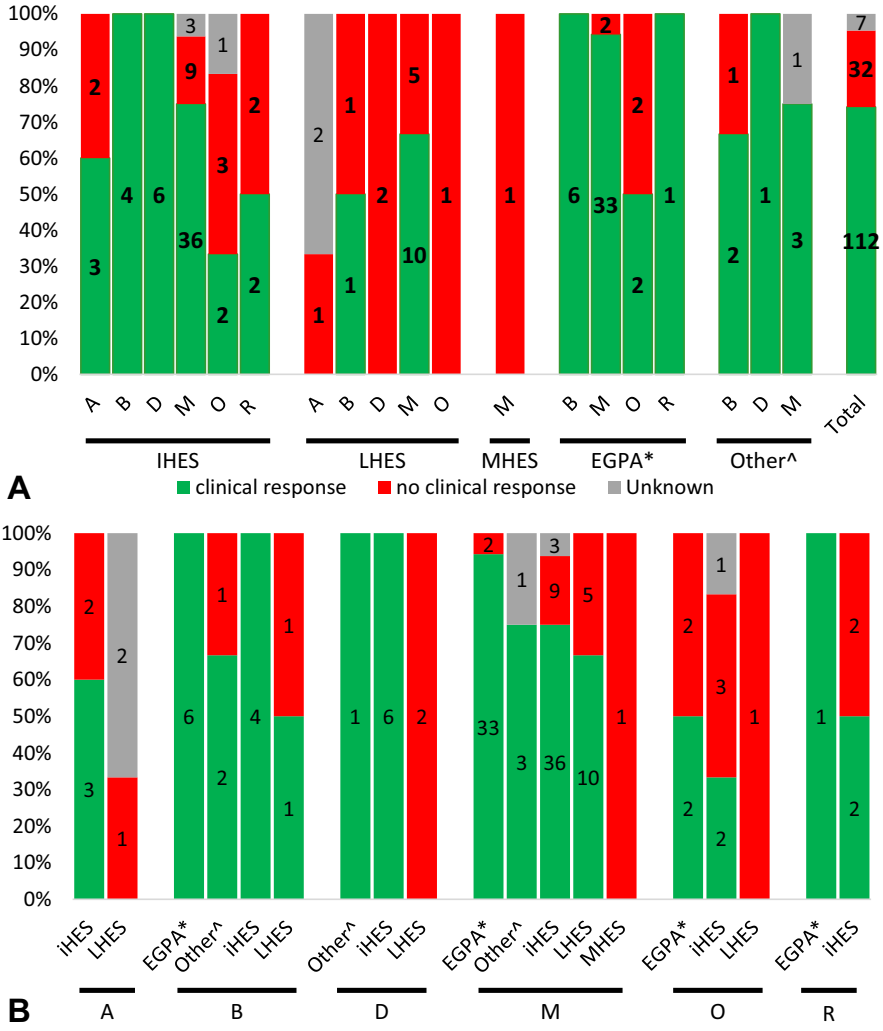

FIGURE 2. Tapering of other hypereosinophilic syndrome (HES) medications while receiving a biologic for each (**A**) HES subgroup and (**B**) biologic. *A*, alemtuzumab; *B*, benralizumab; *D*, dupilumab; **EGPA*, eosinophilic granulomatosis with polyangiitis overlap; *iHES*, idiopathic HES; *LHES*, lymphoid HES; *M*, mepolizumab; *MHES*, myeloid HES; *O*, omalizumab; *^Other*, other overlap; *R*, reslizumab.

omalizumab (eight of 11), and alemtuzumab (seven of eight) were most often administered as first-line biologic therapy, compared with benralizumab (four of 15), dupilumab (four of nine), and reslizumab (one of five).

At the time of each biologic initiation, 93% of patients were already receiving other medications for HES treatment, including systemic glucocorticoids (70%), methotrexate (9%), hydroxyurea (4%), interferon-alfa (2%), and mycophenolate (2%) (see Figure E2 in this article's Online Repository at www.jaci-inpractice.org). An average of 3.4 HES medications (range, 0-9 medications) were used before starting the first biologic. Six patients received more than one of the six studied biologics simultaneously (mepolizumab with omalizumab in four patients, mepolizumab with benralizumab in one patient, and mepolizumab with reslizumab in another).

Hematologic response to biologics

Of the 78 patients who were not already in hematologic remission (defined as AEC <1,000 cells/mm^3) at the time of biologic initiation, 63 (81%) achieved hematologic remission after starting their biologic (Figure 1). More than 90% of those receiving mepolizumab or benralizumab achieved hematologic remission with a lowest median AEC achieved of 86 cells/mm^3 (range, 0-750 cells/mm^3) and 20 cells/mm^3 (range, 0-110 cells/mm^3), respectively (data not shown). In comparison, no patients receiving omalizumab or dupilumab and only half of those receiving alemtuzumab achieved hematologic remission, although the cohort was small and excluded those already in remission at the time of biologic initiation. All five patients who received reslizumab were already in remission at the time of biologic initiation. At the time of data capture, average duration of hematologic remission with a biologic was 33 months (range, 1-188 months), but this is likely an underestimate because most patients studied were still receiving a biologic and in hematologic remission at the time of data collection (data not shown).

Medication-sparing effects of biologics

Overall effects. Most patients receiving a biologic (77%) were able to taper other HES therapies, with observed success rates of 78% (35 of 45) in IHES, 92% (35 of 38) in EGPA, 100% (six of six) in other overlap, and 71% (10 of 14) in LHES. Conversely, the rates were 43% (nine of 21) for LHES, 7% (five

TABLE III. Systemic steroid requirements by HES subgroup and biologic

	# Receiving systemic steroids at biologic initiation, n	# Receiving >5 mg/d of prednisone equivalents at biologic initiation, n	Median dose prior to biologic (mg/day of prednisone equivalents)	Median dose on biologic (mg/d of prednisone equivalents)	Median individual reduction (%)	Median individual reduction, mg	% achieving ≤5 mg/d of prednisone equivalents	% achieving 0 mg/d of prednisone equivalents
By HES subgroup								
IHES	45	39	15.0	2.0	94	10.0	60	47
Alemtuzumab	2	1	10.0	7.5	50	2.5	50	50
Benralizumab	2	2	10.5	0	100	10.5	100	100
Dupilumab	2	1	10.0	0	100	10.0	50	50
Mepolizumab	34	30	20.0	0	100	10.0	62	50
Omalizumab	2	2	15.0	9.0	40	6.0	50	0
Reslizumab	3	3	8.0	6.0	50	4.0	33	0
LHES	16	12	20.0	7.5	48	6.00	31	19
Alemtuzumab	1	1	30.0	20.0	33	10.00	0	0
Benralizumab	1	1	20.0	8.0	60	12.00	0	0
Dupilumab	2	2	20.0	18.5	15	1.5	0	0
Mepolizumab	12	8	17.5	6.5	49	6.0	42	25
Eosinophilic granulomatosis with polyangiitis overlap	39	28	10.0	0.0	100	7.0	82	51
Benralizumab	3	2	10.0	5.0	50	5.0	100	33
Mepolizumab	33	24	10.0	0	100	8.0	85	58
Omalizumab	2	2	20.0	10.0	33	10.0	0	0
Reslizumab	1	0	3.0	3.0	0	0	100	0
Other overlap	5	5	10.0	0.0	100	10.0	100	100
Benralizumab	2	NR	NR	NR	NR	NR	NR	NR
Dupilumab	1	1	10.0	0	100	10.0	100	100
Mepolizumab	2	2	9.5	0	100	9.5	100	100
Total	105	84	15.0	3.0	80	10.0	64	45
By biologic								
Alemtuzumab	3	2	15.0	15.0	33	5.0	33	33
IHES	2	1	10.0	7.5	50	2.5	50	50
LHES	1	1	30.0	20.0	33	10.0	0	0
Benralizumab	8	5	12.5	2.5	80	9.0	63	38
IHES	2	2	10.5	0	100	10.5	100	100
LHES	1	1	20.0	8.0	60	12.0	0	0
EGPA overlap	3	2	10.0	5.0	50	5.0	100	33
Other overlap	2	NR	NR	NR	NR	NR	NR	NR
Dupilumab	5	4	10.0	3.5	65	6.5	40	40
IHES	2	1	10.0	0	100	10.0	50	50
LHES	2	2	20.0	18.5	15	1.5	0	0
Other overlap	1	1	10.0	0	100	10.0	100	100

TABLE III. *(Continued)*

	# Receiving systemic steroids at biologic initiation, n	# Receiving >5 mg/d of prednisone equivalents at biologic initiation, n	Median dose prior to biologic (mg/day of prednisone equivalents)	Median dose on biologic (mg/d of prednisone equivalents)	Median individual reduction (%)	Median individual reduction, mg	% achieving ≤5 mg/d of prednisone equivalents	% achieving 0 mg/d of prednisone equivalents
Mepolizumab	81	64	15.0	0.0	100	10.0	69	51
IHES	34	30	20.0	0	100	10.0	62	50
LHES	12	8	17.5	6.5	49	6.0	42	25
EGPA overlap	33	24	10.0	0	100	8.0	85	58
Other overlap	2	2	9.5	0	100	9.5	100	100
Omalizumab	4	4	15.0	10.0	33	6.0	25	0
IHES	2	2	15.0	9.0	40	6.0	50	0
EGPA overlap	2	2	20.0	10.0	33	10.0	0	0
Reslizumab	4	3	7.0	5.0	25	2.0	50	0
IHES	3	3	8.0	6.0	50	4.0	33	0
EGPA overlap	1	0	3.0	3.0	0	0.0	100	0
Total	105	84	15.0	3.0	80	10.0	64	45

HES, hypereosinophilic syndrome; *IHES*, idiopathic HES; *LHES*, lymphoid HES; *NR*, not reported.

of 67) for IHES, and 10% (five of 52) of overlap patients who required the addition of new HES therapies or up-titration of existing therapies while receiving the biologic, which suggests superior disease control in the latter subgroups (data not shown). Although the small numbers preclude definitive analysis, there was an overall trend for less efficacy, as measured by the ability to taper medications and the need for additional medications with omalizumab use (Figure 2).

Glucocorticoid-sparing effects. At the time of initiation of the biologic, 105 patients were receiving systemic glucocorticoids at a median daily dose of 15 mg (range, 2-266 mg) of prednisone equivalent. This was tapered to a median daily dose of 3 mg (range, 0-30 mg) while patients received the biologic, corresponding to an 80% individualized reduction (Table III). Of the 82 patients on 5 mg/d or greater of prednisone equivalent at the time of biologic initiation, 59% (48 of 82) achieved 5 mg/d or less of prednisone equivalent while receiving a biologic. A reduction in daily dose of prednisone equivalent while receiving a biologic was seen across HES subtypes, including IHES (median individual reduction of 10 mg; 94%), EGPA (7 mg; 100%), other overlap (10 mg; 100%), and LHES (6 mg; 48%). The greatest glucocorticoid-sparing effect was observed in patients receiving mepolizumab and benralizumab, as measured by both the ability to taper to a lower maintenance dose and the magnitude of dose reduction. Overall, 45% of patients were able to taper off glucocorticoids completely while receiving a biologic. In contrast, and although the numbers were small (n = 8), no patients with a pre-biologic daily prednisone equivalent requirement were able to taper off steroids completely while receiving omalizumab or reslizumab.

Organ-specific improvement in signs and symptoms while receiving a biologic

Overall, 92% of symptomatic patients (101 of 110) reported some improvement in HES manifestations while receiving a biologic. Among patients with pulmonary involvement who received mepolizumab (n = 57), 86% showed improvement in one or more pulmonary signs or symptoms (Figure 3). Similar organ-specific improvement with mepolizumab was reported for patients with dermatologic (77%; 27 of 35), gastrointestinal (74%; 14 of 19), and constitutional (67%; 20 of 30) HES manifestations. In contrast, only 10% of patients with neurologic symptoms treated with mepolizumab (two of 20) reported improvement in neurologic manifestations. Similarly, 90% patients receiving benralizumab with pulmonary HES manifestations (nine of 10) reported improvement of these symptoms or clinical signs. Although the numbers were small, omalizumab and alemtuzumab appeared to be generally less effective in symptom reduction with a few possible exceptions, such as improvement in pulmonary signs and symptoms with omalizumab, which was observed in 75% of patients (six of eight). Dupilumab improved dermatologic symptoms in all three overlap HES patients with reported preexisting atopic dermatitis but in neither of the two patients with LHES. Only 11 HES symptoms were reported across five patients receiving reslizumab, with variable response. Cardiac, renal, and rheumatologic manifestations, along with lymphadenopathy or splenomegaly, were less likely to respond to biologic treatment (Figure 3).

	Organ involvement	Symptom improvement on biologic																		
		alemtuzumab			benralizumab			dupilumab			mepolizumab			omalizumab			reslizumab			All biologics		
		%	#	Total	%	#	Total	%	#	Total	%	#	Total	%	#	Total	%	#	Total	%	#	Total
IHES	Cardiac										0%	0	2							0%	0	2
	Constitutional	50%	1	2	100%	1	1				67%	12	18	0%	0	1	50%	1	2	63%	15	24
	Dermatologic	100%	2	2	100%	2	2	100%	2	2	88%	15	17	50%	1	2	50%	1	2	85%	23	27
	Gastrointestinal				100%	1	1	100%	1	1	81%	13	16	50%	1	2				80%	16	20
	LAD or splenomegaly										0%	0	1							0%	0	1
	Neurologic				0%	0	1				13%	1	8							11%	1	9
	Pulmonary	0%	0	1	100%	1	1	100%	2	2	70%	14	20	60%	3	5	50%	1	2	68%	21	31
	Renal	0%	0	1							50%	1	2				0%	0	1	25%	1	4
	Rheumatologic	100%	1	1							38%	3	8	0%	0	1	0%	0	1	36%	4	11
	Vascular										100%	3	3							100%	3	3
	Overall	**57%**	**4**	**7**	**83%**	**5**	**6**	**100%**	**5**	**5**	**65%**	**62**	**95**	**45%**	**5**	**11**	**38%**	**3**	**8**	**64%**	**84**	**132**
LHES	Constitutional	0%	0	1							25%	1	4	0%	0	1				17%	1	6
	Dermatologic				50%	1	2	0%	0	2	50%	6	12	100%	1	1				47%	8	17
	LAD or splenomegaly										0%	0	2							0%	0	2
	Pulmonary	0%	0	1	0%	0	1				86%	6	7							67%	6	9
	Renal										0%	0	1							0%	0	1
	Rheumatologic	0%	0	1	0%	0	1	0%	0	1	0%	0	6	0%	0	1				0%	0	10
	Overall	**0%**	**0**	**3**	**25%**	**1**	**4**	**0%**	**0**	**3**	**41%**	**13**	**32**	**33%**	**1**	**3**				**33%**	**15**	**45**
MHES	Cardiac										0%	0	1							0%	0	1
	LAD or splenomegaly										0%	0	1							0%	0	1
	Overall										**0%**	**0**	**2**							**0%**	**0**	**2**
EGPA Overlap	Cardiac										0%	0	7							0%	0	7
	Constitutional										88%	7	8	100%	1	1	100%	1	1	90%	9	10
	Dermatologic				100%	1	1				100%	5	5	50%	1	2				88%	7	8
	Gastrointestinal				0%	0	2				0%	0	1	50%	1	2				20%	1	5
	Neurologic				100%	1	1				8%	1	12				100%	1	1	21%	3	14
	Pulmonary				100%	6	6				97%	29	30	100%	3	3	100%	1	1	98%	39	40
	Rheumatologic										33%	3	9	0%	0	1				30%	3	10
	Vascular				0%	0	1				50%	1	2							33%	1	3
	Overall				**73%**	**8**	**11**				**62%**	**46**	**74**	**67%**	**6**	**9**	**100%**	**3**	**3**	**65%**	**63**	**97**
Other Overlap	Dermatologic							100%	1	1	100%	1	1							100%	2	2
	Gastrointestinal				0%	0	1				50%	1	2							33%	1	3
	Pulmonary				100%	2	2													100%	2	2
	Renal							0%	0	1										0%	0	1
	Overall				**67%**	**2**	**3**	**50%**	**1**	**2**	**67%**	**2**	**3**							**63%**	**5**	**8**
Entire Cohort	Cardiac		0	0		0	0		0	0	0%	0	10		0	0		0	0	0%	0	10
	Constitutional	33%	1	3	100%	1	1		0	0	67%	20	30	33%	1	3	67%	2	3	63%	25	40
	Dermatologic	100%	2	2	80%	4	5	60%	3	5	77%	27	35	60%	3	5	50%	1	2	74%	40	54
	Gastrointestinal		0	0	25%	1	4	100%	1	1	74%	14	19	50%	2	4		0	0	64%	18	28
	LAD or splenomegaly		0	0		0	0		0	0	0%	0	4		0	0		0	0	0%	0	4
	Neurologic		0	0	50%	1	2		0	0	10%	2	20		0	0	100%	1	1	17%	4	23
	Pulmonary	0%	0	2	90%	9	10	100%	2	2	86%	49	57	75%	6	8	67%	2	3	83%	68	82
	Renal	0%	0	1		0	0	0%	0	1	33%	1	3		0	0	0%	0	1	17%	1	6
	Rheumatologic	50%	1	2	0%	0	1	0%	0	1	26%	6	23	0%	0	3	0%	0	1	23%	7	31
	Vascular		0	0	0%	0	1		0	0	80%	4	5		0	0		0	0	67%	4	6
	Overall	**40%**	**4**	**10**	**67%**	**16**	**24**	**60%**	**6**	**10**	**60%**	**123**	**206**	**52%**	**12**	**23**	**55%**	**6**	**11**	**59%**	**167**	**284**

0% 100%

FIGURE 3. Physician-reported improvement in organ-related signs and symptoms by hypereosinophilic syndrome (HES) subtype and biologic. Percentiles are shown as a colored gradient. *EGPA*, eosinophilic granulomatosis with polyangiitis; *iHES*, idiopathic HES; *LAD,* lymphadenopathy; *LHES*, lymphoid HES; *MHES*, myeloid HES.

Mepolizumab dosing

A total of 103 patients in the study were treated with mepolizumab. In general, there appeared to be little or no correlation between the initial dose used (100, 300, or ≥700 mg monthly) and the likelihood of symptom improvement (Figure 4). Because of higher pre-biologic daily prednisone requirements in patients started on 700 mg or greater compared with 100 mg (median 20 vs 10 mg), the percent reduction in prednisone requirement was similar between groups, as was the percentage of patients achieving less than 5 or 0 mg of daily prednisone use. Median reduction in daily prednisone equivalent with 700 mg or greater dosing was 20 mg (range, 0-30 mg; n = 23) compared with a median reduction of 6.5 mg (range, 0-16 mg; n = 28) for those who started on 100 mg (Table IV).

Benefit of changing biologics or dosing regimens

Of the 24 patients without adequate benefit from their original biologic and who subsequently tried another one, 13 showed clinical improvement (Figure 5). For example, five out of six patients improved clinically with benralizumab after failing mepolizumab. One patient with preexisting atopic dermatitis improved after changing from benralizumab to dupilumab. Of the 36 patients who initially started receiving mepolizumab 100 mg, seven needed to increase to 300 mg and two needed to increase from 300 to 700 mg for symptom control. Conversely, three patients receiving mepolizumab 700 or 750 mg were able to deescalate therapy to 300 mg while maintaining control of the disease. Seven patients were also able to decrease the frequency of mepolizumab administration from every 4 weeks to every 5 to 12 weeks (data not shown).

	Organ involvement	Those with symptom improvement on mepolizumab								
		100 mg			300 mg			≥700 mg		
		%	#	Total	%	#	Total	%	#	Total
IHES	Cardiac	0%	0	1				0%	0	1
	Constitutional	67%	4	6	75%	3	4	63%	5	8
	Dermatologic	80%	4	5	83%	5	6	100%	6	6
	Gastrointestinal	80%	4	5	67%	2	3	88%	7	8
	LAD or splenomegaly							0%	0	1
	Neurologic	0%	0	3	0%	0	2	33%	1	3
	Pulmonary	56%	5	9	100%	2	2	78%	7	9
	Renal	100%	1	1				0%	0	1
	Rheumatologic	0%	0	2	67%	2	3	33%	1	3
	Vascular							100%	3	3
	Overall	**56%**	**18**	**32**	**70%**	**14**	**20**	**70%**	**30**	**43**
LHES	Constitutional				50%	1	2	0%	0	2
	Dermatologic	25%	1	4	60%	3	5	50%	1	2
	Gastrointestinal							0%	0	2
	LAD or splenomegaly	0%	0	1				0%	0	1
	Pulmonary	100%	1	1	50%	1	2	100%	3	3
	Renal							0%	0	1
	Rheumatologic	0%	0	1	0%	0	2	0%	0	3
	Overall	**29%**	**2**	**7**	**45%**	**5**	**11**	**29%**	**4**	**14**
MHES	Cardiac							0%	0	1
	LAD or splenomegaly							0%	0	1
	Overall							**0%**	**0**	**2**
EGPA Overlap	Cardiac	0%	0	4	0%	0	3			
	Constitutional	100%	1	1	80%	4	5	100%	2	2
	Dermatologic	100%	1	1	100%	3	3	100%	1	1
	Gastrointestinal				0%	0	1			
	Neurologic	0%	0	2	11%	1	9	0%	0	1
	Pulmonary	92%	11	12	100%	16	16	100%	2	2
	Rheumatologic	0%	0	1	38%	3	8			
	Vascular				50%	1	2			
	Overall	**62%**	**13**	**21**	**60%**	**28**	**47**	**83%**	**5**	**6**
Other Overlap	Dermatologic	100%	**1**	**1**						
	Gastrointestinal	50%	**1**	**2**						
	Overall	**67%**	**2**	**3**						
Total	Cardiac	0%	0	5	0%	0	3	0%	0	2
	Constitutional	71%	5	7	73%	8	11	58%	7	12
	Dermatologic	64%	7	11	79%	11	14	89%	8	9
	Gastrointestinal	80%	4	5	50%	2	4	70%	7	10
	LAD or splenomegaly	0%	0	1				0%	0	3
	Neurologic	0%	0	5	9%	1	11	25%	1	4
	Pulmonary	77%	17	22	95%	19	20	86%	12	14
	Renal	100%	1	1				0%	0	2
	Rheumatologic	0%	0	4	38%	5	13	17%	1	6
	Vascular				50%	1	2	100%	3	3
	Overall	**56%**	**34**	**61**	**60%**	**47**	**78**	**60%**	**39**	**65**

FIGURE 4. Physician-reported improvement in organ-related signs and symptoms by hypereosinophilic syndrome (HES) subtype and initial mepolizumab dose. Percentiles are shown as a colored gradient. *EGPA*, eosinophilic granulomatosis with polyangiitis; *iHES*, idiopathic HES; *LHES*, lymphoid HES; *MHES*, myeloid HES.

Safety

Biologics were generally well-tolerated (data not shown) except for alemtuzumab, for which five patients reported infusion reactions. Four patients receiving mepolizumab had non–life-threatening reactions leading to discontinuation of three drug in three instances. At the time of data collection, 93 of 121 patients continued to receive a biologic and six were lost to follow-up. Of those who continued to receive a biologic, 80% were in clinical remission at last contact.

DISCUSSION

As a heterogeneous group of diseases unified by the presence of hypereosinophilia and eosinophil-mediated end organ damage, there is strong scientific rationale behind the hypothesis that reducing eosinophilic inflammation with biologics, either directly or indirectly, would have therapeutic benefit in the management of HES. This is most strongly supported by a phase 3 study demonstrating the efficacy of mepolizumab 300 mg every 4 weeks in *FIP1L1*—platelet-derived growth factor receptor

TABLE IV. Systemic steroid requirements in mepolizumab-treated patients by HES subgroup and dosing regimen

HES subtype	Receiving systemic steroids at biologic initiation, n	Receiving >5 mg/d of prednisone equivalents at biologic initiation	Median dose before biologic (mg/d of prednisone equivalents)	Median dose on biologic (mg/d of prednisone equivalents)	Median individual reduction (%)	Median individual reduction, mg	% achieving ≤5 mg/d of prednisone equivalents	% achieving 0 mg/d of prednisone equivalents
HES subgroup								
IHES	34	30	20.0	0.0	100	10.0	62	50
Mepolizumab 100 mg	11	8	10.0	5.0	67	6.0	55	45
Mepolizumab 300 mg	6	13	25.0	2.0	92	10.0	50	17
Mepolizumab >700 mg	17	3	20.0	0	100	20.0	71	65
LHES	11	8	17.5	6.5	49	6.0	36	18
Mepolizumab 100 mg	3	2	15.0	0	100	7.0	67	67
Mepolizumab 300 mg	5	4	20.0	7.0	30	3.0	20	0
Mepolizumab >700 mg	3	2	20.0	10.0	49	10.0	33	0
EGPA overlap	33	24	10.0	0	100	8.0	76	58
Mepolizumab 100 mg	12	8	6.0	0	100	6.0	92	75
Mepolizumab 300 mg	18	13	11.5	3.0	78	8.0	67	44
Mepolizumab >700 mg	3	3	20.0	0	100	20.0	67	67
Other overlap	2	2	9.5	0	80	9.5	86	60
Mepolizumab 100 mg	2	2	9.5	0	100	9.5	100	100
Total	80	64	15.0	0	100	10.0	69	50
Dosing regimen								
Mepolizumab 100 mg	28	22	10.0	0	100	6.5	79	64
IHES	11	10	10.0	5.0	67	6.0	55	45
LHES	3	2	15.0	0	100	7.0	67	67
EGPA overlap	12	8	6.0	0	100	6.0	100	75
Other overlap	2	2	9.5	0	100	9.5	100	100
Mepolizumab 300 mg	29	21	13.0	4.0	68	9.0	59	31
IHES	6	4	25.0	2.0	92	10.0	50	17
LHES	5	4	20.0	7.0	30	3.0	20	0
EGPA overlap	18	13	11.5	3.0	78	8.0	72	44
Mepolizumab >700 mg	23	21	20.0	0	100	20.0	70	57
IHES	17	16	20.0	0	100	20.0	71	65
LHES	3	2	20.0	10.0	49	10.0	33	0
EGPA overlap	3	3	20.0	0	100	20.0	100	66
Total	80	64	15.0	0	100	10.0	69	50

HES, hypereosinophilic syndrome; *IHES*, idiopathic HES; *LHES*, lymphoid HES.

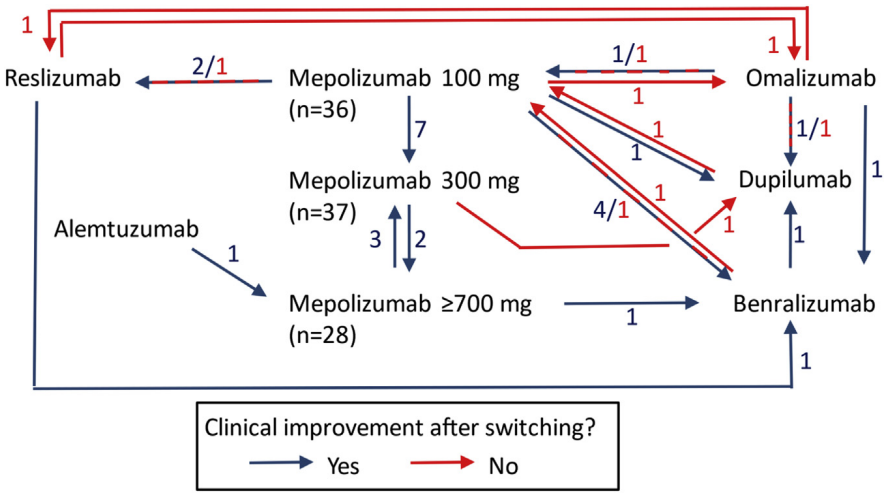

FIGURE 5. Benefits observed after changing biologics or increasing the dose of the same biologic after initial clinical failure.

A—negative HES.[8] As a result of this study, mepolizumab became the first FDA-approved biologic for the treatment of HES in 2020; it had already received FDA approval for the treatment of asthma and EGPA.[9] Phase 2 clinical trials of reslizumab[10] and benralizumab[11] have shown promising results, and a phase 3 trial of benralizumab is ongoing (NCT04191304). Case reports and small series using alemtuzumab,[12-15] dupilumab,[16] and omalizumab[17-19] have also demonstrated benefit in the treatment of some patients with HES.

Unfortunately, to date there are no published studies comparing biologics for the treatment of HES, and there are limited data to guide the biologic choice for the different HES subtypes or even optimal dosing. Furthermore, inclusion and exclusion criteria for clinical trial participation do not cover the entire disease spectrum as experienced in a real-world clinical setting. Outside clinical trials, many factors influence the biologic prescribed, including the geographic availability of drug, physician and patient preferences, affordability, and comorbid conditions. With that in mind, we do not encourage casual interpretations of comparisons among biologics from this study, nor have we applied rigorous statistical analyses to this report. Nevertheless, this study is the largest of its kind and has examined real-world practice data to describe the safety and effects of various biologics used to reduce eosinophilic inflammation for the treatment of HES.

The pathophysiology of HES varies by subtype and is unknown in many patients. This heterogeneity likely underlies the variable response to biologics in our study. Because IL-5 is a key cytokine in eosinophil proliferation and survival,[2] it was unsurprising that targeting IL-5 (mepolizumab and reslizumab) or its receptor (benralizumab) was effective in most patients in reducing blood eosinophils, controlling or improving HES symptoms, and enabling the tapering of other HES medications. Blockade of IL-4 and IL-13 (dupilumab) or IgE binding to its receptor (omalizumab) also demonstrated clinical efficacy, albeit less reliably and less effectively, and typically without inducing hematologic remission of HES. This finding suggests that type 2 inflammation can be an underlying factor beyond eosinophilic inflammation in disease manifestations in some organs in some patients. Alemtuzumab, which binds to CD52 expressed on multiple cell types, including eosinophils, induced a variable response in the small number of HES patients included in this study, but with a greater likelihood for toxicity, consistent with its known side effect profile. The low response rate with alemtuzumab may be confounded by its typical use in only severe or refractory cases of HES.

Interestingly, some patients who failed one biologic went on to achieve control of HES with a different biologic. This highlights the heterogeneous nature of HES and the pharmacologic properties among anti-eosinophil biologics and suggests that more than one biologic could be tried if the first one fails to be effective. Finally, excluding the single MHES patient, it appears that LHES was the least likely HES subtype to respond to a biologic, which is consistent with studies showing that the HES subtype influences treatment responses.[3,20] In general, LHES patients without improvement were also those who required escalation of therapy and were unable to reduce prednisone, which suggests that LHES constitutes a unique subset of biologic nonresponders. This variant may have an underlying pathophysiology that does not respond to the targeting of eosinophils.

Although our study was not designed to make conclusive comparisons among doses of individual biologics, we did not find appreciable differences in clinical response based on the starting doses of mepolizumab, the only biologic for which a range of doses was used. The 300-mg dose given every 4 weeks is approved by the FDA for both EGPA and HES, but our results suggest that alternative doses might be efficacious in some individuals. For example, some patients required dose escalation with mepolizumab to control HES symptoms, whereas other patients were able to retain disease control despite lower mepolizumab dosing or reduced dosing frequency, which suggests that optimal dosing can be individualized.

Limitations of this study include its retrospective nature, the lack of standardization among sites in identifying and treating patients, a limited duration of treatment, and the relatively small numbers of patients who received biologics, especially those other than mepolizumab. Other limitations include those that would confound formal statistical comparisons in an attempt to achieve any correlations or analyses of efficacy among various biologics, HES subsets, and outcomes, because this was purely an observational study. Furthermore, the chronology of regulatory approvals for each drug could influence which biologic was used as first-line,

perhaps leading to a higher proportion of treatment-refractory patients among those receiving drugs with later approval dates. Despite these limitations, some important conclusions are strongly supported. Overall, biologics appear to be safe and effective in the treatment of many HES patients, and those who do not respond to an initial biologic may respond to a different biologic or a higher dose of the same biologic. Ideally, prospective randomized studies are needed to identify which biologic or biologics in combination, and at which dose and dosing frequency, is best suited for the treatment of each HES subtype. Ultimately, a deeper understanding of the mechanisms driving HES should allow a more tailored approach to management.

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TABLE E1. Patient identification and search criteria

Search details	Beth Israel	Cincinnati Children's	Wolfson-Israel	Mayo	MD Anderson	National Jewish	National Institutes of Health	North western	Ohio State University	Brussels	Bern	University of California San Diego	University of Wisconsin Madison
What was the source of patient data?	Patients seen in hospital	Patients seen in hospital	Patients seen in hospital	Patients seen in hospital	Patients seen in hospital	Patients seen in hospital	Natural history protocol for study of eosinophilic diseases (NCT00001406)	Patients seen in hospital	Patients seen in allergy/ immunology and hematology divisions	Patients seen in my division	Only patients seen by me (or someone in my immediate group)	Patients seen in medical system	Only patients seen by me (or someone in my immediate group)
How were patients identified?	From electronic search of medical records	Unbiased electronic search of medical records	Known patients	From electronic search of medical records	From search of pathology archives	From unbiased search of medical records	Research database	From electronic search of medical records	From unbiased search of medical records	From existing database of HES patients	From electronic search of medical records	From electronic search of medical records	From electronic search of medical records
If a medical record or database search was conducted, how was this done?	Individual record review	Automated database search followed by individual record review	Individual record review	Combination of automated electronic search with individual record review	Automatic database search	From electronic search of medical records/ automated database search	Individual record review	Automated database search followed by individual record review	Automated database search followed by individual record review	Individual record review	Automated database search	Electronic medical record automated query	Automated database search
What search logic was used (terms and order)?	"Eosinophilia" then limited to those who received monoclonal therapy	AEC>1,500, individual biologic names	N/A	"Hypereo sinophilia" and "hypereo sinophilic syndrome" automated text search coupled with ICD-9/10 codes for eosinophilia	Eosinophilia and bone marrow, followed by individual patient review	HES idiopathic; HES AND current age ≥12 y AND medication (list of biologics) AND eosinophil count ≥1.5 OR total eosinophils ≥ 1,500 OR absolute eosinophils ≥1.5 OR total circulating eosinophils random ≥1,500 OR absolute eosinophils manual≥1.5 Query included all records in National Jewish Health research database but returned only those that met criteria for the search. Eight	N/A	AEC >1,500, age >12 y, individual biologic names, ICD-9/10 codes for eosinophilia	Records were searched by diagnosis code: ICD-9 codes: 288.3, 530.13, 535.7, 558.4, 693, and 995.1; ICD-10 codes: J18, J45*, J82, D72.1, C95.10, D47.5, T78, K52.81, K20.0, M30.1, and L20.9	Not applicable (all HES patients seen in our department are prospectively recorded in our database)	"Hypereo sinophilia" by individual record review	AEC ≥1,000 (then manual review for AEC ≥1,500); AND list of biologics	"Hypereo sinophilia" followed by individual record review

(continued)

TABLE E1. *(Continued)*

Search details	Beth Israel	Cincinnati Children's	Wolfson-Israel	Mayo	MD Anderson	National Jewish	National Institutes of Health	North western	Ohio State University	Brussels	Bern	University of California San Diego	University of Wisconsin Madison
						were returned, five of which actually qualified upon review							
How many total patient records were searched to identify patients included in the study?	53	35	No search was performed	765	Not sure	The query included all records in National Jewish Health research database but returned only those that met the criteria of the search. eight total were returned, five of which actually qualified upon review	604	Automated search identified 24 patients for individual record review	2,193	In addition to patients included in this study, two subjects received biologics for HES and were not included because they were referred from elsewhere. They came only once for a single dose, with insufficient follow-up data.	We identified 80 patients with hypereo sinophilia treated at dermatology department	47	We identified 80 patients with hypereo sinophilia treated at dermatology department
Were additional patients added based upon personal recall?	No	No	No	No	Not sure	No	No	No	No	No	No	No	No
What was the date range of patients included in the search?	Start January 1, 2017	January 1, 2009 to August 6, 2020	No search. Patients receiving biologics starting in 2014	January 1, 2007 to December 31, 2018	Searched 13 y	2013-2020	April 1983 to October 2020	January 1 2010 to April 2, 2019	January 1, 2000 to January 30, 2019	2004-July 2020 (since availability of the mepoli zumab in compas-sionate use program)	January 1, 2014 to August 31, 2018	August 15, 2012 to July 20, 2020	January 1, 2014 to August 31, 2018

AEC, absolute eosinophil count; *HES*, hypereosinophilic syndrome; *ICD*, International Classification of Diseases; *N/A*, not available.

		Those able to taper or stop other HES therapies on biologic																		
		alemtuzumab			benralizumab			dupilumab			mepolizumab			omalizumab			reslizumab			all biologics		
	HES therapy	%	#	Total	%	#	Total	%	#	Total	%	#	Total	%	#	Total	%	#	Total	%	#	Total
IHES	Azithioprine										100%	1	1							100%	1	1
	Cyclophosphamide				100%	1	1													100%	1	1
	Hydroxyurea										100%	5	5							100%	5	5
	Inhaled corticosteroids							67%	2	3	29%	2	7	100%	0	3	0%	0	1	29%	4	14
	Interferon alpha										100%	1	1							100%	1	1
	Methotrexate							100%	1	1	0%	0	2				100%	1	1	50%	2	4
	Swallowed topical steroids	100%	1	1				100%	2	2	50%	1	2	0%	0	1				67%	4	6
	Systemic steroids	50%	1	2	100%	2	2	100%	2	2	85%	29	34	50%	1	2	67%	2	3	82%	37	45
	Overall	**67%**	**2**	**3**	**100%**	**3**	**3**	**88%**	**7**	**8**	**75%**	**39**	**52**	**17%**	**1**	**6**	**60%**	**3**	**5**	**71%**	55	77
LHES	Hydroxyurea	100%	1	1																100%	1	1
	Inhaled corticosteroids										50%	1	2							50%	1	2
	Interferon alpha	100%	1	1																100%	1	1
	Mycophenolate							0%	0	1				0%	0	1				0%	0	2
	Systemic steroids	100%	1	1	100%	1	1	50%	1	2	75%	9	12							75%	12	16
	Tofacitinib				0%	0	1				0%	0	1							0%	0	2
	Overall	**100%**	**3**	**3**	**50%**	**1**	**2**	**33%**	**1**	**3**	**67%**	**10**	**15**	**0%**	**0**	**1**				**63%**	15	24
EGPA Overlap	Azithioprine				100%	1	1				80%	4	5							83%	5	6
	Inhaled corticosteroids				33%	2	6				19%	4	21	0%	0	3	0%	0	1	19%	6	31
	Interferon alpha										100%	1	1							100%	1	1
	Methotrexate										88%	7	8				0%	0	1	78%	7	9
	Mycophenolate										100%	1	1							100%	1	1
	Swallowed topical steroids				0%	0	1							0%	**0**	**1**				0%	0	2
	Systemic steroids				67%	2	3				94%	31	33	**50%**	**1**	**2**	0%	0	1	87%	34	39
	Overall				**40%**	**4**	**10**				**69%**	**44**	**64**	**17%**	**1**	**6**	**0%**	**0**	**3**	**59%**	49	83
Other Overlap	Swallowed topical steroids				**0%**	**0**	**1**				**100%**	**2**	**2**							**67%**	2	3
	Systemic steroids				**100%**	**2**	**2**		**1**	**1**	**100%**	**2**	**2**							**100%**	5	5
	Overall				**67%**	2	3	**100%**	1	1	**100%**	4	4							**88%**	7	8
Total	Azithioprine				100%	1	1				83%	5	6							86%	6	7
	Cyclophosphamide				100%	1	1													100%	1	1
	Hydroxyurea	100%	1	1							100%	5	5			0				100%	6	6
	Inhaled corticosteroids				33%	2	6	67%	2	3	23%	7	30	0%	0	6	0%	0	2	23%	11	47
	Interferon alpha	100%	1	1							100%	2	2			0				100%	3	3
	Methotrexate					0	0	100%	1	1	70%	7	10			0	50%	1	2	69%	9	13
	Mycophenolate							0%	0	1	100%	1	1	0%	0	1				33%	1	3
	Swallowed topical steroids	100%	1	1	0%	0	2	100%	2	2	75%	3	4	0%	0	2				55%	6	11
	Systemic steroids	67%	2	3	88%	7	8	80%	4	5	88%	71	81	50%	2	4	50%	2	4	84%	88	105
	Tofacitinb				0%	0	1				0%	0	1			0				0%	0	2
	Overall	**83%**	**5**	**6**	**58%**	**11**	**19**	**75%**	**27**	**36**	**72%**	**101**	**140**	**15%**	**2**	**13**	**38%**	**3**	**8**	**66%**	**131**	**198**

0% 100%

FIGURE E2. Reduction of other hypereosinophilic syndrome (HES) therapies while receiving a biologic. Percentiles are shown as a colored gradient. *EGPA*, eosinophilic granulomatosis with polyangiitis; *iHES*, idiopathic HES; *LHES*, lymphoid HES.