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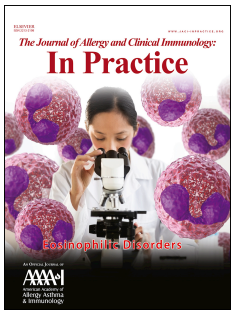

An International, Retrospective Study of Off-Label Biologic Use in the Treatment of Hypereosinophilic Syndromes

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

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Abstract:

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 either directly or indirectly impact eosinophilic inflammation for the treatment of HES.

Methods: Retrospective data from 13 centers were collected via an online REDCap data repository. Inclusion criteria included 1) peripheral eosinophil count ≥1500/mm^3 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 alpha), omalizumab (anti-IgE), alemtuzumab (anti-CD52), dupilumab (anti-IL-4 receptor alpha), or reslizumab (anti-IL-5) outside of 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 on daily systemic glucocorticoids at the time of a biologic initiation and were able to reduce their 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 out of 24 patients had clinical improvement after switching biologics, and 9 patients responded to increasing the dose of mepolizumab after lack of response to a lower dose.

Conclusion: Biologics may offer a safer treatment alternative to existing therapies for HES, although the optimal dosing and choice for each subtype of HES remains to be determined. Limitations of this study include its retrospective nature and inter-site differences in data collection and availability of each biologic.

Highlights box

1. What is already known about this topic?

   Hypereosinophilic syndromes are rare diseases with few treatment options.

2. What does this article add to our knowledge?

   Provides retrospective data on the efficacy and safety of biologics for the treatment of HES.

3. 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.

Key words: hypereosinophilic syndrome, eosinophil, eosinophilic granulomatosis with polyangiitis, biologic

Abbreviations:

AEC: Absolute eosinophil count

EGPA: Eosinophilic granulomatosis with polyangiitis

FIP1L1: Factor interacting with PAPOLA and CPSF1

HES: Hypereosinophilic syndrome

IHES: Idiopathic hypereosinophilic syndrome

LHES: Lymphoid hypereosinophilic syndrome

MHES: Myeloid hypereosinophilic syndrome

PDGFRA: Platelet-derived growth factor receptor A

Introduction:

Hypereosinophilic syndromes (HES) are a rare group of heterogeneous diseases sharing the common features of a sustained peripheral blood eosinophil count of ≥1,500 cells per mm^3, 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 the *FIP1L1-PDGFRA* fusion on chromosome 4, that 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 *PDGFR*-associated MHES but has little to no efficacy in non-myeloid forms of HES, targeted treatment options remain limited and management hinges on off-label use of immunosuppressants, mainly systemic glucocorticoids alone or in conjunction with glucocorticoid-sparing agents that are often poorly tolerated and/or ineffective(3). Biologics that reduce eosinophilic inflammation either directly or indirectly offer a possible alternative treatment modality. Although mepolizumab is currently the only FDA-approved biologic for the treatment of HES, a number of additional biologics that impact eosinophilic inflammation are used either 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 examine 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 the criteria for HES, evaluated prior to December 2020 at 13 participating institutions (10 US, 2 Europe, and 1 in Israel) with expertise in eosinophilic disorders, were included in the study. Patients were identified either by a search of medical records or from an existing database of hypereosinophilic syndrome patients (Table S1). Inclusion criteria were as follows: 1) blood absolute eosinophil count ≥1,500 cells/mm^3 (2 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 of 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 Lymphoid HES (LHES); 2) Overlap HES included those with single organ involvement; 3) Patients categorized as eosinophilic granulomatosis with polyangiitis (EGPA) met at least 4 out of 6 criteria for EGPA as described by the American College of Rheumatology (5); 4) A diagnosis of myeloid HES (MHES) required the detection of a molecular genetic alteration known to be associated with eosinophilic myeloid neoplasms, 5) All others were categorized as idiopathic HES (IHES).

Data collection

Study data were collected and managed using REDCap electronic data capture tools (6,7). REDCap (Research Electronic Data Capture) is a secure, web-based software platform designed to support data capture for research studies, providing 1) an intuitive interface for validated data capture; 2) audit trails for tracking 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 electronic medical record searches depending on the site (Figure S1). Clinical and laboratory data were collected via chart review and entered without identifiers, in accordance with local institutional review boards (Figure S1). No duplicates were identified on the basis of date of birth, sex, and clinical characteristics. Hematologic response to a biologic was defined as a reduction in peripheral blood absolute eosinophil count to <1,000 cells/mm^3. Clinical response was defined as improvement in HES manifestations or ability to taper other HES medications without 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 was entered for the respective symptom or finding.

Statistical analysis

Percent reduction in daily prednisone equivalents was calculated as the difference in pre-treatment and post-treatment prednisone divided by pre-treatment prednisone requirements.

Results:

Patient characteristics

Of the 121 patients enrolled (range of 1-37 subjects per site at 13 different sites), 54 (45%) were male sex (Table 1). The median age at initiation of first biologic was 45 years (range 10-86 years). The peak recorded peripheral blood absolute eosinophil count (AEC) ranged from 1,510 to 89,000 cells/mm^3 with a geometric mean of 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-CD8-, CD3+CD4+CD8+ or CD3+CD4+CD25+ T cells in the peripheral blood were documented in 1 patient each and were confirmed to have a clonal TCR rearrangement by PCR. 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, 1 was positive for JAK2 V617F and was classified as having MHES. The overlap HES subgroup comprised 46 patients, of which 40 met ACR criteria for EGPA and 6 had single organ eosinophilic involvement (3 gastrointestinal, 2 dermatologic, 1 pulmonary). The remaining 58 patients were categorized as IHES. Overall, 85 HES patients had pulmonary manifestations were most common (n=85) 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 1 and 2). Patient characteristics were largely similar across biologics, including the age at biologic initiation, race, ethnicity, and peak AEC. Mepolizumab was the most common biologic received (103 out of 151 courses, or 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 of a placebo-controlled trial, of which 30 were received on an open-label extension after completion of a placebo-controlled trial, 3 were initially received on an open-label trial, 18 through compassionate use or expanded access programs, 95 by provider prescription, and for 5 patients, the context of the biologic course was not reported (data not shown). Of the 33 patients on an open label trial or extension, 31 continued to receive the same biologic (8 remain on trial, 20 on expanded access, 3 by provider prescription) and 2 changed to a different biologic. Mepolizumab (97 of 103),

omalizumab (8 of 11) and alemtuzumab (7 of 8) were most often administered as first line biologic therapy compared to benralizumab (4 of 15), dupilumab (4 of 9) and reslizumab (1 of 5).

At the time of each biologic initiation, 93% of patients were already on other medications for HES treatment including systemic glucocorticoids (70%), methotrexate (9%) hydroxyurea (4%), interferon alpha (2%) and mycophenolate (2%) among others (Figure S2). An average of 3.4 HES medications (range 0-9) were used prior to 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 1 patient and mepolizumab with reslizumab in another).

Hematologic Response to Biologics

Sixty-three of the 78 patients (81%) who were not already in hematologic remission (defined as AEC <1,000 cells/mm^3) at the time of biologic initiation achieved hematologic remission after starting their biologic (Figure 1). Greater than 90% of those on mepolizumab or benralizumab achieved hematologic remission with a lowest median AEC achieved of 86 cells/mm^3 (range 0-750) and 20 cells/mm^3 (range 0-110), respectively (data not shown). In comparison, none of the patients on omalizumab or dupilumab, and only half of those receiving alemtuzumab, achieved hematologic remission, although the cohort is small and excludes those already in remission at the time of biologic initiation. All 5 patients who received reslizumab were already in remission at the time of biologic initiation. At the time of data capture, the average duration of hematologic remission on a biologic was 33 months (range 1 - 188), but this is likely an underestimate because the majority of patients studied were still on a biologic and in hematologic remission at the time of data collection (data not shown).

Medication-Sparing Effects of Biologics

Overall effects

The majority (77%) of patients receiving a biologic 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% (6 of 6) in Other Overlap and 71% (10 of 14) in LHES. Conversely, 43% (9 of 21) of LHES, 7% (5 of 67) of IHES and 10% (5 of 52) of Overlap patients required the addition of new HES therapies or up-titration of existing therapies while on their biologic, suggesting superior disease control in the latter subgroups (data not shown). While small numbers preclude definitive analysis, there was an overall trend for less efficacy, as measured by the ability to taper medications and need for additional medications, with omalizumab use (Figure 2).

Glucocorticoid-Sparing Effects

At the time of initiation of the biologic, 105 patients were on 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 on the biologic, corresponding to an 80% individualized reduction (Table 3). Of the 82 patients on >5 mg per day of prednisone equivalent at the time of biologic initiation, 59% (48 of 82) achieved ≤5 mg per day of prednisone equivalent while on a biologic. A reduction in daily dose of prednisone equivalent on 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 completely taper off glucocorticoids while on 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 completely taper off steroids while receiving omalizumab or reslizumab.

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

Overall, 92% (101 of 110) of symptomatic patients reported some improvement in HES manifestations while on 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% (2 of 20) of patients with neurologic symptoms treated with mepolizumab had reported improvement in neurologic manifestations. Similarly, 90% (9 of 10) patients on benralizumab with pulmonary HES manifestations reported improvement of these symptoms or clinical signs. While the numbers were small, omalizumab and alemtuzumab appeared 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% (6 of 8) of patients. Dupilumab improved dermatologic symptoms in all 3 Overlap HES patients with reported preexisting atopic dermatitis but in neither of the two patients with LHES. Only 11 HES symptoms were reported across 5 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).

Mepolizumab dosing

A total of 103 patients in the study were treated with mepolizumab. In general, there appeared to be little to no correlation between the initial dose used (100, 300 or ≥700 mg monthly) and the

likelihood of symptom improvement (Figure 4). Due to higher pre-biologic daily prednisone requirements in patients started on ≥700 mg compared to 100 mg (median 20 vs 10 mg), the percent reduction in prednisone requirement was similar between the two groups, as was the percentage of patients achieving less than 5 mg or 0 mg of daily prednisone usage. The median reduction in daily prednisone equivalent on ≥700 mg dosing was 20 mg (range 0-30 mg, n=23) compared to a median reduction of 6.5 mg (range 0-16 mg, n=28) for those who started on 100 mg (Table 4).

Benefit of changing biologics or dosing regimens

Of the 24 patients without adequate benefit on their original biologic and who subsequently tried another biologic, 13 showed clinical improvement (Figure 5). For example, 5 out of 6 patients improved clinically on benralizumab after failing mepolizumab. One patient with pre-existing atopic dermatitis improved after changing from benralizumab to dupilumab. Of the 36 patients who initially started on mepolizumab 100 mg, 7 needed to increase to 300 mg and two patients needed to increase from 300 mg to 700 mg for symptom control. Conversely, 3 patients on mepolizumab 700 mg or 750 mg were able to de-escalate therapy to 300 mg while maintaining control of their 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).

Safety

Biologics were generally well tolerated (data not shown) except for alemtuzumab, for which 5 patients reported infusion reactions. Four patients on mepolizumab had non-life-threatening reactions leading to discontinuation of drug in 3 instances. At the time of data collection, 93 of

the 121 patients remained on a biologic and 6 were lost to follow up. Of those that remained on 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-PDGFRA*-negative HES (8). As a result of this study, mepolizumab became the first FDA-approved biologic for the treatment of HES in 2020, having 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, there are no published studies comparing biologics for the treatment of HES to date, and there are limited data to guide 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 of 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 between 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. Given that IL-5 is a key cytokine in eosinophil proliferation and survival (2), it was not surprising that targeting IL-5 (mepolizumab, reslizumab) or its receptor (benralizumab) was effective in the majority of 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 their HES on a different biologic, highlighting the heterogeneous nature of HES and the pharmacologic properties among anti-eosinophil biologics, suggesting 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, consistent with studies showing that HES subtype influences treatment responses (3,20). In general, LHES patients without improvement were also those who required escalation of therapy and were not able to reduce prednisone, suggesting that LHES constitutes a unique subset of biologic non-

responders. This variant may have an underlying pathophysiology that does not respond to the targeting of eosinophils.

While our study was not designed to make conclusive comparisons between 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 were used. Even though the 300 mg dose given every 4 weeks is now FDA-approved for both EGPA and HES, our results suggest that alternative doses might be efficacious in some individuals. For example, some patients required dose escalation on mepolizumab to control HES symptoms, while other patients were able to retain disease control despite lower mepolizumab dosing or reduced dosing frequency, suggesting that optimal dosing can be individualized.

Limitations of this study include its retrospective nature, the lack of standardization between 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 given that 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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Figure Legends

Figure 1. Hematologic remission (defined as AEC <1,000 cells/mm3) status by biologic administered. A=alemtuzumab, B=benralizumab, D=dupilumab, O=omalizumab, M=mepolizumab, R=reslizumab

Figure 2. Tapering of other HES medications while on a biologic for each HES subgroup (panel A) and biologic (panel B). A=alemtuzumab, B=benralizumab, D=dupilumab, M=mepolizumab, O=omalizumab, R=reslizumab. *EGPA=EGPA Overlap, ^Other=Other Overlap.

Figure 3. Physician reported Improvement in organ-related signs and symptoms by HES subtype and biologic. Percentiles shown on colored gradient

Figure 4. Physician reported Improvement in organ-related signs and symptoms by HES subtype and by initial mepolizumab dose. Percentiles shown on colored gradient.

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

	Patients (n)	Sex (M/F)	Age at first biologic, median (range)	Peak eosinophil count (cell/mm³) Geometric mean (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 Childrens	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**

Table 1. Patient characteristics by participating site. *Drug not available at this site. A=alemtuzumab, B=benralizumab, D=dupilumab, O=omalizumab, M=mepolizumab, R=reslizumab

	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)**
Sex (%F)	50%	60%	67%	53%	64%	40%	**55%**
Race (%)							
-White	75%	80%	89%	84%	91%	100%	**85%**
-Black	13%	7%	-	3%	-	-	**4%**
-Asian	-	-	-	6%	-	-	**4%**
-unknown	13%	13%	11%	8%	9%	-	**9%**
Ethnicity							
-Non-Hispanic	75%	87%	89%	87%	91%	100%	**87%**
-Hispanic	25%	7%	11%	5%	9%	-	**7%**
-unknown	-	7%	-	8%	-	-	**6%**
Peak AEC mean cells/mm^3 (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)							
-IHES	63% (5)	27% (4)	67% (6)	46% (48)	55% (6)	80% (4)	**48% (73)**
-LHES	37% (3)	13% (2)	22% (2)	15% (15)	9% (1)	-	**15% (23)**
-MHES	-	-	-	1% (1)	-	-	**1% (1)**
-EGPA Overlap	-	40% (6)	-	34% (35)	36% (4)	20% (1)	**31% (46)**
-Other Overlap	-	20% (3)	11% (1)	4% (4)	-	-	**5% (8)**

Table 2. Patient characteristics by biologic administered. LHES defined by abnormal clonal T cell population identified by flow cytometry. MHES required detection of a mutation associated with eosinophilic myeloid neoplasms. *****Data in this column taken from first initiation of a biologic.

A

	On Systemic Steroids at Biologic Initiation	On > 5 mg/day of Prednisone Equivalents at Biologic Initiation	Median dose prior to biologic (mg/day of prednisone equivalents)	Median dose on biologic (mg/day of prednisone equivalents)	Median Individual Reduction (%)	Median Individual Reduction (mg)	% Achieving ≤5 mg/day of Prednisone Equivalents	% Achieving 0 mg/day of Prednisone Equivalents
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	0.0	100%	10.5	100%	100%
Dupilumab	2	1	10.0	0.0	100%	10.0	50%	50%
Mepolizumab	34	30	20.0	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%
EGPA 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	0.0	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%	0.0	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	0.0	100%	10.0	100%	100%
Mepolizumab	2	2	9.5	0.0	100%	9.5	100%	100%
Total	**105**	**84**	**15.0**	**3.0**	**80%**	**10.0**	**64%**	**45%**

B	On Systemic Steroids at Biologic Initiation (n)	On > 5 mg/day of Prednisone Equivalents at Biologic Initiation	Median dose prior to biologic (mg/day of prednisone equivalents)	Median dose on biologic (mg/day of prednisone equivalents)	Median Individual Reduction (%)	Median Individual Reduction (mg)	% Achieving ≤5 mg/day of Prednisone Equivalents	% Achieving 0 mg/day of Prednisone Equivalents
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	0.0	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	0.0	100%	10.0	50%	50%
LHES	2	2	20.0	18.5	15%	1.5	0%	0%
Other overlap	1	1	10.0	0.0	100%	10.0	100%	100%
Mepolizumab	**81**	**64**	**15.0**	**0.0**	**100%**	**10.0**	**69%**	**51%**
IHES	34	30	20.0	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	0.0	100%	8.0	85%	58%
Other overlap	2	2	9.5	0.0	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%**

Table 3. Systemic steroid requirements by HES subgroup (panel A) and by biologic (panel B). NR = not reported

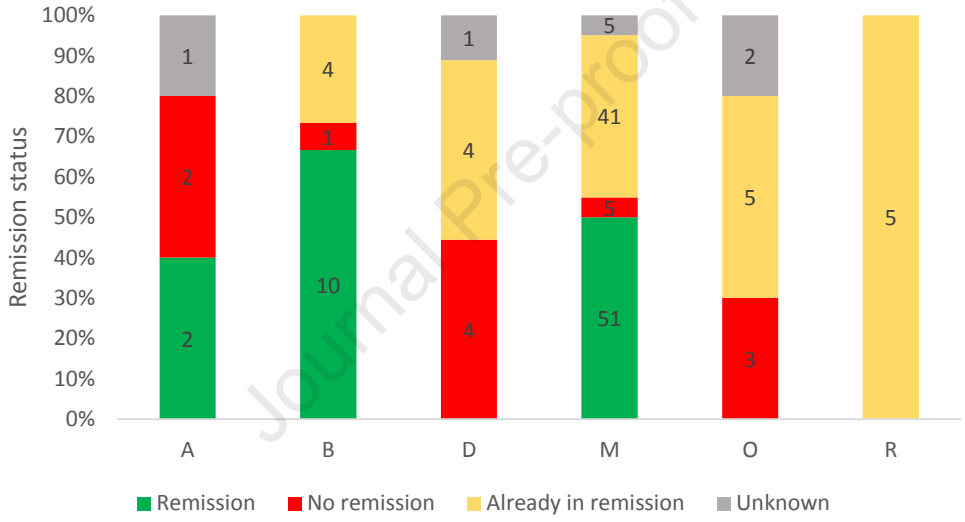
A

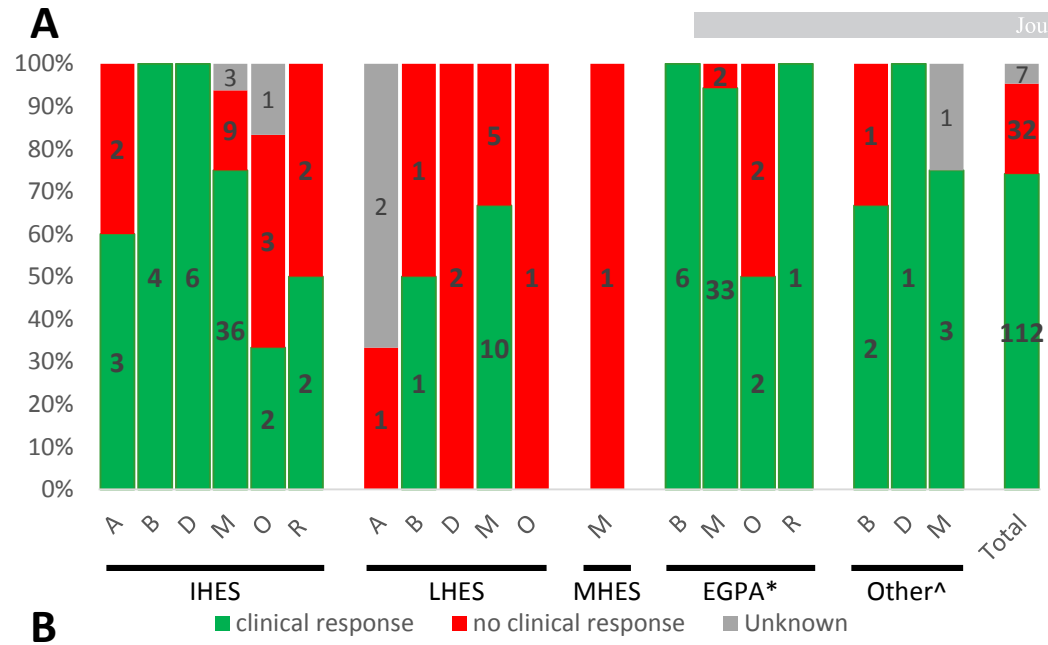
	On Systemic Steroids at Biologic Initiation (n)	On > 5 mg/day of Prednisone Equivalents at Biologic Initiation	Median dose prior to biologic (mg/day of prednisone equivalents)	Median dose on biologic (mg/day of prednisone equivalents)	Median Individual Reduction (%)	Median Individual Reduction (mg)	% Achieving ≤5 mg/day of Prednisone Equivalents	% Achieving 0 mg/day of Prednisone Equivalents
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	0.0	100%	20.0	71%	65%
LHES	**11**	**8**	**17.5**	**6.5**	**49%**	**6.0**	**36%**	**18%**
Mepolizumab 100 mg	3	2	15.0	0.0	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**	**0.0**	**100%**	**8.0**	**76%**	**58%**
Mepolizumab 100 mg	12	8	6.0	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	0.0	100%	20.0	67%	67%
Other Overlap	**2**	**2**	**9.5**	**0.0**	**80%**	**9.5**	**86%**	**60%**
Mepolizumab 100 mg	2	2	9.5	0.0	100%	9.5	100%	100%
Total	**80**	**64**	**15.0**	**0.0**	**100%**	**10.0**	**69%**	**50%**

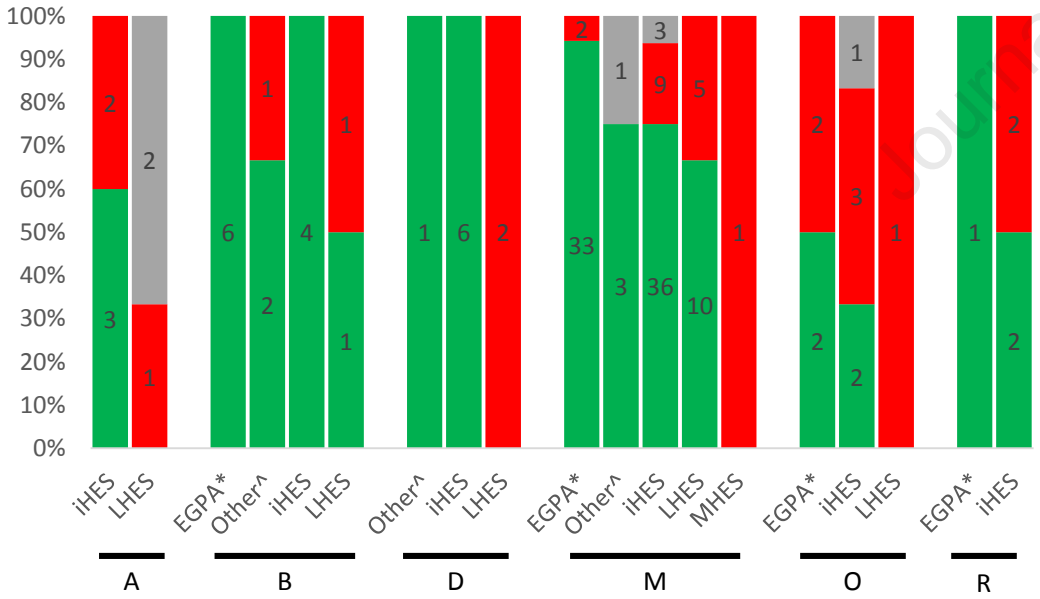
B

	On Systemic Steroids at Biologic Initiation (n)	On > 5 mg/day of Prednisone Equivalents at Biologic Initiation	Median dose prior to biologic (mg/day of prednisone equivalents)	Median dose on biologic (mg/day of prednisone equivalents)	Median Individual Reduction (%)	Median Individual Reduction (mg)	% Achieving ≤5 mg/day of Prednisone Equivalents	% Achieving 0 mg/day of Prednisone Equivalents
Mepolizumab 100 mg	**28**	**22**	**10.0**	**0.0**	**100%**	**6.5**	**79%**	**64%**
IHES	11	10	10.0	5.0	67%	6.0	55%	45%
LHES	3	2	15.0	0.0	100%	7.0	67%	67%
EGPA Overlap	12	8	6.0	0.0	100%	6.0	100%	75%
Other Overlap	2	2	9.5	0.0	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**	**0.0**	**100%**	**20.0**	**70%**	**57%**
IHES	17	16	20.0	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	0.0	100%	20.0	100%	66%
Total	**80**	**64**	**15.0**	**0.0**	**100%**	**10.0**	**69%**	**50%**

Table 4. Systemic steroid requirements in mepolizumab-treated patients by HES subgroup (panel A) and by dosing regimen (panel B) expressed in mg of prednisone equivalents per day.







	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

	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**