

Hypereosinophilic syndrome: A multicenter, retrospective analysis of clinical characteristics and response to therapy

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Background: Hypereosinophilic syndrome (HES) is a heterogeneous group of rare disorders defined by persistent blood eosinophilia $\geq 1.5 \times 10^9/L$, absence of a secondary cause, and evidence of eosinophil-associated pathology. With the exception of a recent multicenter trial of mepolizumab (anti-IL-5 mAb), published therapeutic experience has been restricted to case reports and small case series.

Objective: The purpose of the study was to collect and summarize baseline demographic, clinical, and laboratory characteristics in a large, diverse cohort of patients with HES and to review responses to treatment with conventional and novel therapies.

Methods: Clinical and laboratory data from 188 patients with HES, seen between January 2001 and December 2006 at 11 institutions in the United States and Europe, were collected retrospectively by chart review.

Results: Eighteen of 161 patients (11%) tested were Fip1-like 1-platelet-derived growth factor receptor α (*FIP1L1-PDGFR α*)

mutation—positive, and 29 of 168 patients tested (17%) had a demonstrable aberrant or clonal T-cell population. Corticosteroid monotherapy induced complete or partial responses at 1 month in 85% (120/141) of patients with most remaining on maintenance doses (median, 10 mg prednisone equivalent daily for 2 months to 20 years). Hydroxyurea and IFN- α (used in 64 and 46 patients, respectively) were also effective, but their use was limited by toxicity. Imatinib (used in 68 patients) was more effective in patients with the *FIP1L1-PDGFR α* mutation (88%) than in those without (23%; $P < .001$). **Conclusion:** This study, the largest clinical analysis of patients with HES to date, not only provides useful information for clinicians but also should stimulate prospective trials to optimize treatment of HES. (J Allergy Clin Immunol 2009;123:1016-1022.)

Key words: Eosinophil, hypereosinophilic syndrome, *FIP1L1-PDGFR α*

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Abbreviations used

CEL: Chronic eosinophilic leukemia
 FP: Fip1-like 1–platelet-derived growth factor receptor α
 GM: Geometric mean
 HES: Hypereosinophilic syndrome
 L-HES: Lymphocytic variant hypereosinophilic syndrome
 TARC: Thymus and activation-related chemokine
 TCR: T-cell receptor rearrangement PCR

Hypereosinophilic syndrome (HES) is a diverse group of rare disorders defined by the presence of persistent peripheral blood eosinophilia $\geq 1.5 \times 10^9/L$, the absence of a secondary cause of eosinophilia, and evidence of eosinophil-associated end organ damage.¹ The clinical heterogeneity of HES has long been recognized²; however, it is only recently that the techniques have become available to identify subtypes of HES with different underlying etiologies. The 2 best described of these subtypes are lymphocytic variant HES (L-HES),³ in which the underlying cause of the eosinophilia is secretion of eosinophilopoietic cytokines by T lymphocytes, and myeloproliferative HES/chronic eosinophilic leukemia (CEL),^{4,5} most commonly caused by an interstitial deletion in chromosome 4. These subtypes are associated with dramatic differences in clinical presentation, prognosis, and responses to therapy.⁶ The availability of new targeted therapies, including tyrosine kinase inhibitors and humanized mAbs, have only increased the importance of developing a better understanding of the etiologies and pathogenesis of HES, because these may be predictors of treatment response.

Despite the fact that a wide variety of agents have been used for the treatment of HES, published therapeutic experience has been largely restricted to case reports and small case series, the exception being a recently published multicenter trial of the monoclonal anti-IL-5 antibody, mepolizumab, as a steroid-sparing agent in HES.⁷ The lack of published data is in large part a result of the paucity of affected patients as well as the heterogeneity of presenting symptoms. This retrospective, multicenter analysis sought to collect and summarize the baseline demographic, clinical, and laboratory characteristics in a large, diverse cohort of patients with HES and to review responses to treatment with both conventional and novel therapies.

METHODS

Patients meeting diagnostic criteria for HES,⁶ evaluated between January 2001 and December 2006 at 11 participating institutions with expertise in the evaluation of eosinophilic disorders, were included in the study. Inclusion criteria were documentation of a peripheral eosinophil count of $\geq 1.5 \times 10^9/L$ and signs or symptoms of end organ involvement for which another etiology could not be found. Patients with neoplasms (other than Fip1-like 1–platelet-derived growth factor receptor α [FP]-positive CEL), biopsy-positive Churg-Strauss vasculitis, single organ eosinophilic diseases without blood eosinophilia, and overlap syndromes⁶ were excluded from the study. Patients were enrolled consecutively at each site beginning with patients seen at an initial or follow-up visit in December 2006 and proceeding backward in time until 50 patients were included from a given site or the year 2001 was reached.

Clinical and laboratory data pertaining to baseline characteristics and treatment responses were collected after chart review, entered without identifiers into a database, and compiled for analysis (see this article's Online Repository at www.jacionline.org). Potential duplicates were removed on the basis of a combination of factors, including birth year, sex, and clinical

features. Institutional review board approval and informed consent were obtained as required by each institution.

All 188 patients underwent detailed evaluation at the contributing clinical sites, including a complete history, physical examination, and laboratory evaluation (Table I). Parameters previously shown or suspected to have prognostic significance in HES, such as peak eosinophil count, serum IL-5, total IgE, vitamin B₁₂, tryptase, and thymus and activation-related chemokine (chemokine ligand 17) (TARC [CCL17]) levels, were assessed. Results of FP mutation analysis (by nested PCR or fluorescence *in situ* hybridization) and assessment of T-cell clonality and phenotype by peripheral blood flow cytometry and/or T-cell receptor rearrangement PCR (TCR) were also included in the analysis. Although whole blood flow cytometry techniques and antibody panels varied among the sites, CD3, CD4, and CD8 antibodies, which detect the most common aberrant phenotypes in L-HES (CD3⁺CD4⁺ and CD3⁺CD4⁺CD8⁺),⁸ were included in all panels. Serum TARC levels were determined by using commercially available ELISA kits from R&D Systems Europe (Abbingdon, UK; Erasme Hospital, Brussels, Belgium; Technical University, Munich, Germany; University of Leicester, United Kingdom; detection limit, 7 pg/mL) or by ELISA from Thermo Fisher Scientific (Waltham, Mass; Laboratory of Parasitic Diseases, National Institutes of Health, Bethesda, Md; detection limit, 0.8 pg/mL). Serum IL-5 levels were determined by using commercially available ELISA kits from BD Biosciences Pharmingen (San Jose, Calif) or R&D Systems (Minneapolis, Minn; Cincinnati Children's Hospital Medical Center, Ohio; Erasme Hospital; University of Leicester; Hôpital Foch, Suresnes, France; Mayo Clinic, Rochester, Minn; Harvard Medical School, Boston, Mass; University of Utah, Salt Lake City; detection limit, 7.8 pg/mL) or by ELISA by Thermo Fisher Scientific (Laboratory of Parasitic Diseases; detection limit, 0.8 pg/mL). Laboratory information, including results of FP mutation testing, T-cell studies, and serum TARC levels, was requested on all patients; however, because of the retrospective nature of the study, all results were not available in all cases. Normal values were defined as follows: IgE <100 IU/mL, serum IL-5 <14.1 pg/mL, tryptase <11.5 ng/mL, vitamin B₁₂ <950 pg/mL, and TARC <500 pg/mL.

Clinical responses at 1 month of treatment (full, partial, or no response) were recorded, as well as the maintenance dose, the maximal dose (for prednisone only), and whether each drug was given as monotherapy. Complete responses were defined as decrease of the eosinophil count to the normal range ($0-0.5 \times 10^9/L$) and symptomatic improvement after 1 month of treatment. Partial responses were defined as a decrease of the eosinophil count, but not to the normal range, and/or symptomatic improvement after 1 month of treatment. No response was defined as a stable or increasing eosinophil count and no symptomatic improvement after 1 month of treatment.

Statistical analysis

Nonparametric comparisons of group means were made by using the Mann-Whitney *U* test. Proportions were compared by using the Fisher exact test. A *P* value less than .05 was considered significant for all tests.

RESULTS**Baseline characteristics**

Of the 188 patients evaluated, 104 were male (55%), and 84 were female (45%). The median age at diagnosis was 45 years of age (range, 6-85 years). The peak recorded absolute eosinophil counts ranged from 1.5 to $400 \times 10^9/L$ with a geometric mean (GM) peak eosinophil count of $6.6 \times 10^9/L$ (Table I). Of the 161 patients tested for the FP mutation, 18 (11%), all of whom were male, were positive. Of the 168 patients who were evaluated for clonal or aberrant populations of T cells, 29 (17%; 15 male and 14 female) were positive by PCR ($n = 14$), flow cytometry ($n = 3$), or both ($n = 12$). These patients were classified as having L-HES. There were 4 patient deaths reported during the study period, 2 of which were thought to be secondary to HES (because of eosinophilic heart disease).

TABLE I. Baseline characteristics of patients

Center*	Number of patients	Sex (male/female)	Age at diagnosis (y), median (range)	GM peak eosinophil count $\times 10^3/L$ (range)
BRU	22	12/10	48 (15-81)	6.29 (2.0-16.7)
MUN	8	5/3	43 (12-65)	3.37 (1.5-8.32)
LEIC	14	10/4	62 (30-78)	10.52 (2.12-80.90)
BALT	15	8/7	46 (23-85)	5.86 (2.0-59.75)
CIN	21	10/11	37 (15-56)	5.45 (1.5-42.0)
MINN	16	7/9	54 (9-69)	5.91 (1.89-29.02)
BOS	7	4/3	45 (23-59)	7.30 (3.5-14.39)
SLC	13	8/5	30 (6-74)	11.34 (2.4-85.0)
BETH	39	12/14	42 (16-69)	8.98 (2.2-400)
BER	14	6/8	54 (8-69)	5.18 (1.5-340)
SUR	19	9/10	43 (14-65)	5.61 (1.7-31.60)
Total	188	105/82	45 (6-85)	6.602 (1.5-400)

Sex distribution, median age at diagnosis, and GM peak eosinophil count are provided for each of the participating centers. *BALT*, Johns Hopkins Hospital, Baltimore, Md; *BER*, University of Bern, Switzerland; *BETH*, Laboratory of Parasitic Diseases, National Institutes of Health, Bethesda, Md; *BOS*, Harvard Medical School, Boston, Mass; *BRU*, Erasme Hospital, Brussels, Belgium; *CIN*, Cincinnati Children's Hospital Medical Center, Ohio; *LEIC*, University of Leicester, United Kingdom; *MINN*, Mayo Clinic, Rochester, Minn; *MUN*, Technical University of Munich, Germany; *SLC*, University of Utah, Salt Lake City; *SUR*, Hôpital Foch, Suresnes, France.

Serum tryptase levels were reported for 123 patients (66%) and ranged from 1 to 131 ng/mL (GM, 7.6 ng/mL). Elevated serum tryptase levels were significantly more common in patients with the FP mutation (9/11; 82%) than in patients who tested negative for the mutation (21/105; 20%; $P = .001$). Furthermore, among the 30 patients with elevated levels, the GM tryptase level was greater in the FP-positive patients (31 vs 19 ng/mL; $P = .03$). Serum vitamin B₁₂ levels were reported for 120 patients and ranged from 156 to 10,995 pg/mL (GM, 632 pg/mL). Elevated serum vitamin B₁₂ levels were also more common in the FP-positive patients (range, 401-10,955 pg/mL, and present in 13/14; 93%) versus FP-negative patients (range, 156-2000 pg/mL and present in 20/106; 18%; $P < .0001$). Elevated serum tryptase and/or B₁₂ levels were uncommon in patients with L-HES, occurring in only 3 of 25 and 1 of 22 patients tested, respectively.

Serum TARC levels were reported for 82 patients from 4 centers (see Methods) and ranged from 22 to 150,100 pg/mL (GM, 769 pg/mL). Serum TARC levels were elevated in 75% (12/16) of patients with L-HES compared with 36% (24/66) of patients without a clonal or aberrant T-cell population ($P = .0017$). Furthermore, GM serum TARC levels in the subset of patients with elevated levels were significantly increased in patients with L-HES compared with those without (GM, 12,979 vs 3406 pg/mL; $P = .02$). Serum IgE levels were elevated in 83 of 150 patients tested (55%). In the 135 patients who were also evaluated for clonal or aberrant T-cell populations, serum IgE was elevated in 19 of 28 (68%) patients with L-HES and 56 of 107 (52%) in whom a clonal or aberrant population was sought but not found ($P < .0001$). Only 1 patient in the FP group had an elevated IgE level, and none had elevated serum TARC levels.

Serum IL-5 levels were assessed in 107 patients and ranged from undetectable to 377 pg/mL. IL-5 levels were elevated in 28 of 107 (26%) patients: 6 patients with L-HES, 1 patient with the FP mutation, and 21 patients with HES in whom FP mutation analysis and at least 1 test for T-cell clonality/phenotype had been performed and were negative.

Data pertaining to initial clinical presentation were collected for all patients (Fig 1, A; see this article's Table E1 in the Online Repository at www.jacionline.org). The most common presenting manifestations of HES were dermatologic (70/188; 37%), followed by pulmonary (47/188; 25%) and gastrointestinal (25/188; 14%). Less than 5% (9/188) of patients had cardiac manifestations at the time of diagnosis. Of note, 6% (11/188) of patients presented with clinically asymptomatic eosinophilia identified on laboratory testing performed for unrelated reasons.

Dermatologic involvement was also the most common subsequent clinical manifestation of HES and was reported in 69% (130/188) of patients. This was followed in frequency by pulmonary (44%) and gastrointestinal (38%) manifestations (Fig 1, B). Cardiac disease unrelated to hypertension, atherosclerosis, or rheumatic disease was reported in 20% (37/188) of the patients. The frequency of cardiac disease was similar in patients with and without the FP mutation (4/18, 22%, vs 33/170, 19%, respectively).

Treatment

Corticosteroids. Corticosteroids have long been the mainstay of therapy for HES, although the dosing has not been standardized.^{6,9} In this series, 179 (95%) patients were treated

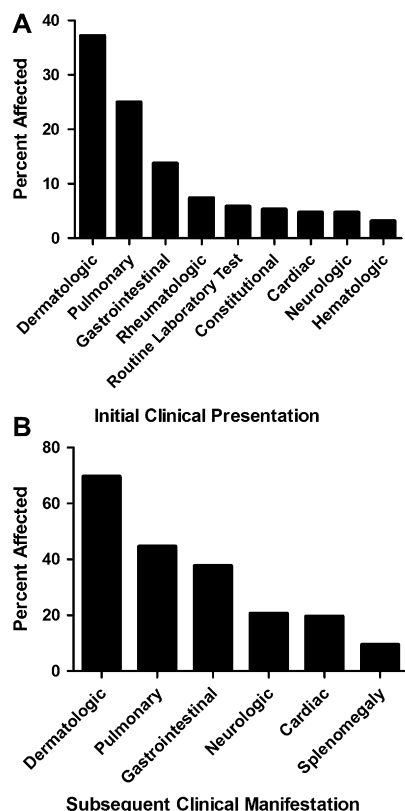


FIG 1. Clinical manifestations of HES. The clinical manifestations at initial presentation (A) and at the time of the retrospective analysis (B) are shown as the percentage of patients with evidence of organ involvement referable to a given category. Reported manifestations in each of the categories are listed in this article's Table E2 in the Online Repository at www.jacionline.org.

with corticosteroids, most of whom (163/188; 81%) received corticosteroids as initial therapy. The median maximal daily dose of prednisone (or prednisone equivalent) was 40 mg (range, 5-625 mg). Most patients (130/179; 72%) were maintained on corticosteroids for some time, ranging from 2 months to 30 years, with a median maintenance dose of 10 mg daily (range, 1-40 mg/d).

Of the 141 of 188 (75%) patients who received corticosteroid monotherapy, 120 (85%) experienced a complete or partial response after 1 month of treatment (Fig 2, A). When corticosteroids were used in combination therapy (most often because of failure or corticosteroid toxicity), the most frequent second agents added were hydroxyurea (36 patients) and IFN- α (24 patients). Responses (complete or partial) were achieved in 69% (25/36) of patients receiving hydroxyurea and corticosteroids and 75% (18/24) of patients treated with IFN- α and corticosteroids.

Prednisone was discontinued in 42% (75/179) of patients. The most frequently cited reasons for discontinuation were lack of efficacy (40%) and "other" (40%; Fig 2, B). The most common reasons for the response "other" were efficacy of another drug, most frequently imatinib or anti-IL-5 antibody ($n = 12$), and disease remission ($n = 12$).

Elevated serum IgE and TARC levels have been associated with corticosteroid responsiveness in patients with HES.^{10,11} Serum IgE levels were elevated in 77 of 142 (54%) patients who received corticosteroid therapy and for whom serum IgE

levels were available. The percentage of patients with elevated IgE was comparable in patients who responded to steroids and those who did not (73/129, 57%, vs 4/13, 31%; $P = .09$, Fisher exact test). Similarly, GM serum IgE levels were similar in patients with a complete (125 IU/mL), partial (222 IU/mL), or lack of response (70 IU/mL) to corticosteroid therapy (Fig 3, A).

Serum TARC levels were elevated in 41 of 82 (50%) patients who received corticosteroid therapy and for whom levels were available. GM TARC levels were significantly elevated in patients who responded to corticosteroids compared with nonresponders (979 vs 242; $P = .01$), and serum TARC levels >10,000 pg/mL ($n = 11$) were reported only among prednisone responders (Fig 3, B).

Hydroxyurea. Thirty-four percent (64/188) of patients were treated with the oral cytotoxic agent hydroxyurea, with a median maximum daily dose of 1000 mg (range, 500-2000 mg). Eighteen patients received hydroxyurea as monotherapy, of whom 6 (33%) achieved a complete response and 7 (39%) a partial response (Fig 2, A). Hydroxyurea was discontinued in the majority of patients (49/64; 77%), primarily because of a lack of efficacy (23/49; 47%) and medication intolerance secondary to treatment-related side effects (21/49; 43%; Fig 2, B).

IFN- α . Approximately one quarter of the patients (46/188) were treated with IFN- α , with a median maximal dose of 14 million units per week (range, 3-40 million units per week). Only 12 patients received IFN- α as monotherapy, of whom 2 (17%) achieved a complete response and 4 (33%) a partial response at 1 month (Fig 2, A). IFN- α was discontinued in all but 6 patients (87%). The most common reasons for drug discontinuation were medication intolerance (20/40; 50%), lack of efficacy (14/40; 36%), and cost (1/40; 3%; Fig 2, B).

Cyclosporine. Eleven of 188 (6%) patients were treated with cyclosporine (median maximal daily dose, 200 mg; range, 150-500 mg). Of the 5 patients who received cyclosporine monotherapy, 1 patient achieved a complete response (20%), and 2 patients (40%) achieved partial responses (Fig 2, A). The medication was discontinued in 9 of 11 patients (82%), including the patient who responded completely for reasons of medication intolerance (Fig 2, B).

Imatinib. The tyrosine-kinase inhibitor imatinib was initiated in 68 of 188 patients (36%), of whom 17 were known to be positive for the FP mutation. The median maximal dose used was 400 mg daily (range, 100 mg twice weekly to 600 mg daily). Of the 31 patients who received imatinib monotherapy, 20 of 31 (65%) achieved a complete response and 2 of 31 (6%) a partial response (Fig 2, A). Of the FP-positive patients, 15 of 17 (88%) responded completely, and 2 (12%) had no response.^{12,13} In contrast, only 10 of 43 (23%) FP-negative patients who received imatinib experienced a complete ($n = 6$) or partial ($n = 4$) response ($P < .0001$ compared with the FP-positive patients).

Imatinib was discontinued in 41 of 68 patients, mostly because of lack of efficacy (33/41; 80%; Fig 2, B). The remaining 8 of 41 patients discontinued imatinib therapy because of medication intolerance (4 patients), unspecified reasons (2 patients), the initiation of an anti-IL-5 clinical trial (1 patient), or the desire to have children (1 patient).

Anti-IL-5 antibody. A total of 62 of 188 (33%) patients received at least 1 dose of anti-IL-5 mAb therapy with mepolizumab (GlaxoSmithKline, Philadelphia, Pa; 750 mg/mo; $n = 59$), reslizumab (Ception, Malvern, Pa; 1-3 mg/kg/mo; $n = 2$), or both ($n = 1$). Of the 15 patients who received mepolizumab

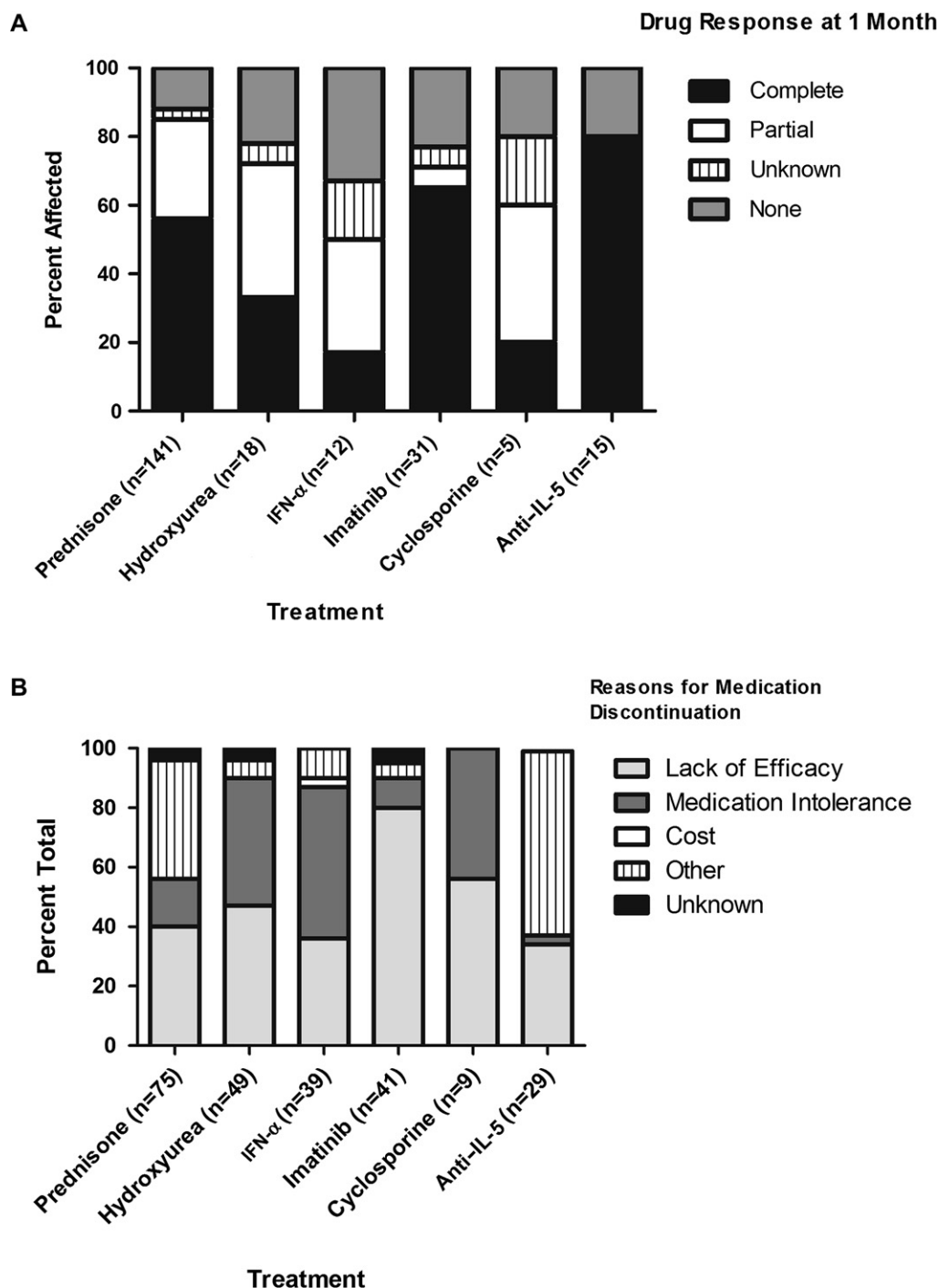


FIG 2. Response to treatment. The bars represent response rates after 1 month of therapy (A) and reasons for drug discontinuation (B). Responses were defined as complete (normalization of absolute eosinophil count [AEC] and clinical symptom improvement), partial (reduction of AEC, but not to normal levels, and/or improvement in symptoms), or no response (neither reduction of AEC nor improvement in symptoms).

monotherapy, 12 of 15 (80%) achieved a complete response 1 month after the initiation of therapy (Fig 2, A). As has been previously reported,¹⁷ 2 patients received reslizumab monotherapy, both of whom responded after 1 month of therapy. The remaining 45 patients were treated concomitantly with mepolizumab and corticosteroids. Thirty-four of 45 (76%) responded completely after 1 month of mepolizumab, and an additional 5 (11%) had a partial response.

Although anti-IL-5 therapy was discontinued in 29 of 62 (47%) patients, the most frequent cause for discontinuation (18 patients; 62%) was the completion of a clinical trial (listed as “other”; Fig 2, B). An additional 10 patients (34%) discontinued because of lack of efficacy. Only 1 patient discontinued anti-IL-5 treatment because of medication intolerance.

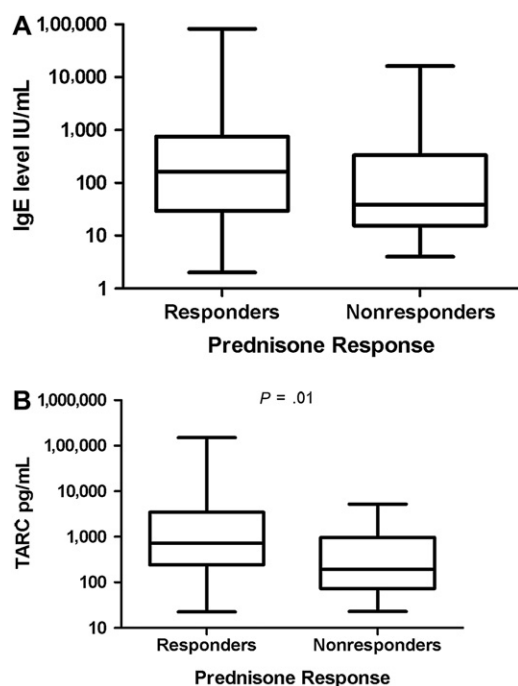


FIG 3. Association of serum TARC but not serum IgE levels with prednisone responsiveness. Serum IgE (**A**) and TARC (**B**) levels for prednisone responders ($n = 129$ and 75 , respectively) and nonresponders ($n = 13$ and 8 , respectively) are shown by using box-and-whisker plots. The *whiskers* represent the minimum and maximum values and the *horizontal lines* represent the lower quartile, median, and upper quartile.

Other agents. Several other medications were used for treatment of HES (Table E1); however, too few patients were treated to draw conclusions for individual agents.

DISCUSSION

One of the major problems with previously reported series of patients with HES has been referral bias, with single centers more likely to see patients with end organ manifestations that fall within the area of expertise of a particular subspecialty interested in HES. This has been compounded by the tendency to publish cases of the most severely affected patients, a disproportionate number of whom, in retrospect, were likely FP-positive. Patients in the current series were referred to groups with international recognition in the diagnosis and treatment of HES, composed of a wide variety of subspecialty physicians. Consequently, the data compiled are more likely to represent the true spectrum of HES. The major limitation of this study was the retrospective design and resultant lack of standardization of laboratory studies between the different sites. Despite these limitations, however, a number of interesting conclusions can be drawn.

In contrast with the marked (9:1) male predominance of HES reported in the literature, the ratio of male to female subjects in the current study was 11:8. This likely reflects the fact that FP-positive patients, who are almost exclusively male, were overrepresented in previous series, and it confirms data from recent studies in which FP-positive patients were excluded.⁷ Similarly, early assessments of the relative prevalence of end organ manifestations were gleaned from case reports and small series and tended to overestimate more serious consequences of

HES, including cardiac and neurologic involvement.² In the current series, the most common presenting manifestations of HES were dermatologic, pulmonary, and gastrointestinal. Cardiac and neurologic complications did occur but were relatively uncommon at the initial presentation. Earlier diagnosis and the availability of better therapies likely contributed to the improved HES patient outcomes in the current series. It is important to note that 11 of the 188 patients presented with asymptomatic eosinophilia found on routine laboratory testing. Of these, 2 were found to have FP mutation–positive CEL, a condition associated with high morbidity and mortality (as many as 50% at 5 years) in the absence of imatinib therapy.⁵ These findings highlight the importance of a comprehensive evaluation and close follow-up of patients presenting with unexplained hypereosinophilia.

There has been considerable controversy regarding the prevalence of L-HES and the FP mutation among patients meeting criteria for HES. Early studies likely overestimated the prevalence of these 2 entities because of selection bias.^{3,4} More recently, the prevalence of the FP mutation has been estimated at 14% in a retrospective analysis of 81 patients with primary eosinophilia $\geq 1.5 \times 10^9/L$ who underwent bone marrow examination.¹⁴ The prevalence of FP-positive patients was slightly lower in our study (10%), possibly because of the inclusion of patients in whom a bone marrow examination was not deemed necessary (ie, less likely to have myeloproliferative disease). The association between elevated serum vitamin B₁₂ and tryptase levels and the presence of the FP mutation was confirmed in the current study. Of note, extremely high levels of serum vitamin B₁₂ (>2000 pg/mL) were observed only in the FP-positive group, suggesting that this may be a more discriminating biomarker of myeloproliferative HES.

Confirmation of L-HES is complex, ideally involving both lymphocyte phenotyping and TCR analysis. Consequently, differences in technique as well as the characteristics of the population studied likely account for the variability in the reported prevalence of L-HES, ranging from 14% to 31%.^{3,15,16} In the current study, 17% of patients who were tested had clonal/abnormal populations of T cells detected by PCR or flow cytometry. Although it is debatable whether L-HES can be diagnosed on the basis of a clonal population identified by PCR in the absence of a detectable aberrant phenotype by flow cytometry (8.3% of the patients in the current study), the fact that some patients with clonal TCR rearrangement patterns have strikingly elevated serum TARC and/or IgE levels¹¹ suggests that aberrant T-cell populations not identified using current antibody panels may be responsible for the eosinophilia in these patients. Nevertheless, a prospective trial using standardized techniques is clearly necessary to obtain an accurate assessment of the prevalence of L-HES.

Early efficacy studies and extensive clinical experience have proven corticosteroids to be the first-line agent for the treatment of FP-negative HES.⁶ Although the previously reported association between prednisone responsiveness and elevated serum IgE levels¹⁰ was not confirmed in this study, TARC levels were significantly higher in patients who responded to prednisone. There was no difference between the serum IL-5 levels in patients who responded to prednisone and those who failed to respond (data not shown). Most patients were maintained on low-dose to moderate-dose prednisone therapy (5–20 mg daily). Although this would seem to indicate that the need for alternative therapies is small, the study questionnaire was not designed to detect steroid

toxicities that did not lead to drug discontinuation. Furthermore, the majority of corticosteroid-responsive patients went on to receive a second-line agent, consistent with a higher rate of steroid toxicity and/or resistance than is evident from the collected data.

In the past 5 to 10 years, HES subtypes have been defined, and a number of new, targeted agents have been developed, including imatinib mesylate and humanized mAbs to IL-5. The restriction of this retrospective study to patients seen after 2001 was intended to maximize inclusion of data on these newer agents. As expected, imatinib was extremely effective in FP-positive patients, with resistance described in only 2 patients. The 23% response rate in FP-negative patients is more difficult to interpret because the database did not include sufficient information to distinguish patients with myeloproliferative features who may be more likely to respond to imatinib. Although anti-IL-5 therapy was well tolerated with an overall response rate of 80%, all patients received this agent in clinical trials, the majority of which required patients to be steroid-responsive^{7,13} or were limited to a small number of doses.¹⁷ Consequently, conclusions regarding the long-term efficacy of anti-IL-5 therapy and the most appropriate patients for treatment await further study.

In summary, HES is a rare group of disorders for which unbiased information on demographics, clinical manifestations, and treatment responses is scarce. Although the current study has limitations because of its retrospective design, it represents the largest multicenter study of unselected patients with HES to date. As such, it not only provides useful information for clinicians involved in the care of patients with HES but also ideally will stimulate carefully designed prospective trials for the treatment of this disorder.

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Key messages

- Classically defined HES is a heterogeneous group of varied disorders, the majority of which remain idiopathic.
- Corticosteroids are extremely effective in the treatment of FP-negative HES, but their use may be limited by side effects.
- Carefully designed prospective trials are required to advance the diagnosis and treatment of HES.

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QUESTIONNAIRE

Instructions

Rules for patient inclusion:

1. Patients with >1500 eosinophils/mm³ and signs or symptoms of end organ involvement for whom another etiology cannot be found. Patients with neoplasms (other than FP-positive CEL), biopsy-positive Churg-Strauss vasculitis, single organ eosinophilic diseases (eosinophilic cystitis, eosinophilic gastroenteritis, chronic eosinophilic pneumonia), and overlap syndromes should not be included.
2. Patients should be enrolled consecutively beginning with patients seen at an initial or follow-up visit in December 2006 and proceeding backward in time until you have included 50 patients or reached the year 2001.
3. Patients whose cases have been published elsewhere and patients you only saw once in consultation may be included as long as you have enough information.

Instructions for the table:

The first 3 sections (demographics, clinical manifestations, and laboratory values) should be relatively self-explanatory. If laboratory tests prior to drug therapy are not available, please mark NA (not available). For the maximum eosinophil count, you may use a count from an outside lab (ex. you are seeing the patient on steroids with a normal count but have a reports from the referring physician).

For the drug therapies, please list all drugs they have received, whether you prescribed them or not.

Timing refers to the order in which drugs were started: 1 = first, 2 = second,... If two drugs were started simultaneously, they should get the same number.

In the monotherapy column, mark Y if the drug was given alone and N if it was added to another therapy. If given with another therapy, please indicate what that therapy was in parentheses.

The code for reason is as follows:

- 1 = lack of efficacy
- 2 = drug toxicity
- 3 = cost
- 4 = other (please specify)

Please note: some extra columns were added to the prednisone section to try to get a better handle on how this is prescribed.

1. Please **add an additional column for each medication** to indicate drug nonresponse, partial response, or complete response in the first 1 month of treatment (coded as 0, 1, 2 respectively).
 - a. Nonresponse, "0" = In first 1 month of treatment there is no decrease in eosinophil count and no symptom improvement
 - b. Partial response, "1" = In first 1 month of treatment, eosinophil count decreases but not to normal range and/or symptoms improve
 - c. Complete response, "2" = In first 1 month of treatment, eosinophil count decreases to normal range and symptoms improve
2. Please identify the method that clonality was determined—either flow or PCR. (Some institutions have already provided this.)
3. Please verify that IgE units are IU/mL.

Baseline information		Demographics		Clinical manifestations		Laboratory findings	
		Patient initials		Cardiac		(if not available, enter NA)	
		Gender		Dermatologic		Peak eos/mm ³	
		Year of birth		Pulmonary		Serum B ₁₂ (pg/mL)	
		Year of Diagnosis		Hematologic		Serum IgE (IU/mL)	
		Year of last visit		Neurologic		Serum IL-5 (pg/mL)	
				Gastrointestinal		Serum tryptase	
				Splenomegaly		(ng/mL)	
				Other (specify)		FP	
						T-cell clonality	
						Method of clonality	
						detection (flow or PCR)	
						TARC	
Treatment	Prednisone (Y or N)	Hydroxyurea (Y or N)	IFN (Y or N)	Imatinib (Y or N)	Cyclosporine A (Y or N)	Anti-IL-5 (Y or N)	Other (specify)
	Timing	Timing	Timing	Timing	Timing	Timing	Timing
	Monotherapy?	Monotherapy?	Monotherapy?	Monotherapy?	Monotherapy?	Monotherapy?	Monotherapy?
	Max dose	Max dose	Max dose	Max dose	Max dose	Max dose	Max dose
	Maintenance dose	Length of therapy	Length of therapy	Length of therapy	Length of therapy	Length of therapy	Length of therapy
	Intermittent?	Discontinued?	Discontinued?	Discontinued?	Discontinued?	Discontinued?	Discontinued?
	Length of therapy	Reason	Reason	Reason	Reason	Reason	Reason
	Discontinued?	Response	Response	Response	Response	Response	Response
	Reason						
	Response						

TABLE E1. Clinical manifestations on initial presentation

Clinical manifestations on initial presentation	Total no. of patients* affected	Description
Cardiac	9	Congestive heart failure (4), valvular abnormality (1), cardiomyopathy (1), pericardial effusion (1), myocarditis (2)
Hematologic	6	Deep venous thrombosis (4), anemia (1), superficial thrombophlebitis (1)
Dermatologic	70	Urticaria (6), angioedema (15), pruritis (26), dermatitis (26), erythroderma (1), bullous lesions (1), eosinophilic cellulitis (Well syndrome) (3), unspecified edema (8), mucosal erosions (3)
Pulmonary	47	Asthma (21), sinusitis (9), rhinitis (2) , cough (19), dyspnea (11), recurrent upper respiratory infection (2), pulmonary infiltrates (4), pleural effusion (1)
Gastrointestinal	26	Abdominal pain (9), vomiting (6), diarrhea (5)
Rheumatologic	14	Arthralgia (3), myalgia (9), arthritis (1), myositis (1)
Neurologic	9	Vertigo (2), paresthesia (4), change in mentation (1), aphasia (1), visual disturbances (3)
Constitutional	10	Fever (3), weight loss (6), malaise (7), fatigue (4), night sweats (3), flulike illness (2)
Routine laboratory test	11	Incidental abnormality found on routine laboratory testing (11)

*Some patients had multiple simultaneous manifestations.

TABLE E2. Other agents used for the treatment of HESs

Treatment	No. of patients	Received as monotherapy	Discontinued	Reason
Alemtuzumab	2	1	1	Lack of efficacy (1)
Azathioprine	8	4	4	Lack of efficacy (2), toxicity (2)
Cyclophosphamide	3	0	3	Lack of efficacy (2), toxicity (1)
Cladribine	1	0	1	Lack of efficacy (1)
Dapsone	4	4	3	Lack of efficacy (2), toxicity (1)
Efalizumab	2	2	1	Lack of efficacy (1)
Fludarabine	1	1	1	NA
IFN- γ	1	1	1	NA
Intravenous immunoglobulin	1	0	1	Anaphylaxis
Omalizumab	1	0	1	Lack of efficacy (1)
6-Mercaptopurine	2	0	2	Lack of efficacy (2)
Methotrexate	11	3	10	Lack of efficacy (8), toxicity (1), other (1)
Mycophenolate mofetil	4	2	3	Lack of efficacy (3)
Hydroxychloroquine	1	0	1	Lack of efficacy (1)
PUVA	4	1	4	Lack of efficacy (4)
Thalidomide	2	2	2	Lack of efficacy (2)
VP-16	3	1	3	Lack of efficacy (3)

NA, Not applicable; PUVA, psoralen + ultraviolet A light therapy; VP-16, etoposide phosphate.