Peripheral blood eosinophilia and hypersensitivity reactions among patients receiving outpatient parenteral antibiotics

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Background: Although drug-induced peripheral eosinophilia complicates antimicrobial therapy, little is known about its frequency and implications.

Objective: We aimed to determine the frequency and predictors of antibiotic-induced eosinophilia and subsequent hypersensitivity reactions (HSRs).

Methods: We evaluated a prospective cohort of former inpatients receiving intravenous antibiotic therapy as outpatients with at least 1 differential blood count. We used multivariate Cox proportional hazards models with time-varying antibiotic treatment indicators to assess the effect of demographic data and antibiotic exposures on eosinophilia and subsequent HSRs, including documented rash, renal injury, and liver injury. Possible drug rash with eosinophilia and systemic symptoms (DRESS) syndrome cases were identified and manually validated.

Results: Of 824 patients (60% male; median age, 60 years; median therapy duration, 41 days), 210 (25%) had eosinophilia, with median peak absolute eosinophil counts of 726/mL (interquartile range, 594-990/mL). Use of vancomycin, penicillin, rifampin, and linezolid was associated with a higher hazard of having eosinophilia. There was a subsequent HSR in 64 (30%) of 210 patients with eosinophilia, including rash (n = 32), renal injury (n = 31), and liver injury (n = 13). Patients with eosinophilia were significantly more likely to have rash (hazard ratio [HR], 4.16; 95% CI, 2.54-6.83; $P < .0001$) and renal injury (HR, 2.13; 95% CI, 1.36-3.33; $P = .0009$) but not liver injury (HR, 1.75; 95% CI, 0.92-3.33; $P = .09$). Possible DRESS syndrome occurred in 7 (0.8%) of 824 patients; 4 (57%) were receiving vancomycin.

Conclusions: Drug-induced eosinophilia is common with parenteral antibiotics. Although most patients with eosinophilia do not have an HSR, eosinophilia increases the hazard rate of having rash and renal injury. DRESS syndrome was more common than previously described. (J Allergy Clin Immunol 2015;■■■:■■■-■■■.)

Key words: *Allergy, antibiotic, drug, eosinophilia, hypersensitivity, drug rash with eosinophilia and systemic symptoms syndrome, vancomycin, metronidazole, outpatient parenteral antimicrobial therapy*

Medications are the most common cause of peripheral blood eosinophilia in developed nations.[1] Substantial tissue damage is unlikely to occur with an absolute eosinophil count (AEC) of less than 1500/mL, and expert opinion supports that isolated eosinophilia can be monitored without medication changes. However, drug-induced eosinophilia often prompts clinician concern for an impending hypersensitivity reaction (HSR).[2,3] The basis of clinical concern is that peripheral blood eosinophilia is associated with many severe HSRs, including organ-specific reactions (eg, immune-mediated nephritis, hepatitis, and pneumonitis) and severe cutaneous adverse reactions (SCARs; eg, Stevens-Johnson syndrome [SJS]/toxic epidermal necrolysis [TEN] and drug rash with eosinophilia and systemic symptoms [DRESS] syndrome).[4-11] However, despite the association of eosinophilia with these HSRs, studies have yet to define whether peripheral blood eosinophilia is truly a risk factor for the development of HSRs.

Although almost any drug can be implicated to cause HSRs, the risk is largest with antimicrobial agents.[12-15] Today, antibiotic use approaches 60% among inpatients, with many infections requiring extended parenteral antimicrobial therapy.[16-19] Inpatients requiring prolonged intravenous treatment can receive continued intravenous antimicrobial treatment at home or in a skilled nursing facility through an outpatient parenteral antimicrobial therapy (OPAT) program.[20] Although prior studies of patients receiving OPAT have evaluated tolerability, adverse drug reactions, and some allergic reactions,[20] research has not evaluated drug-induced peripheral eosinophilia or captured organ-specific injury that is more likely immune-mediated/allergic (an HSR) rather than toxic in nature.

Among antimicrobials, asymptomatic eosinophilia has most commonly been described with penicillins, cephalosporins, and flouroquinolones.[1,21] However, these same classes of antibiotics are also implicated in patients with HSRs.[10,22,23] We aimed to identify the frequency of and risk factors for development of peripheral blood eosinophilia and HSRs among a population of monitored outpatients receiving antimicrobial therapy.

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Abbreviations used
AEC: Absolute eosinophil count
DRESS: Drug rash with eosinophilia and systemic symptoms
HR: Hazard ratio
HSR: Hypersensitivity reaction
IQR: Interquartile range
OPAT: Outpatient parenteral antimicrobial therapy
SCAR: Severe cutaneous adverse reaction
SJS: Stevens-Johnson syndrome
TEN: Toxic epidermal necrolysis

METHODS

OPAT cohort and study sample

Inpatients who were discharged from the Massachusetts General Hospital (Boston, Massachusetts) with at least 2 weeks of remaining parenteral therapy and who were seen by the Infectious Disease Service during their admission were enrolled prospectively in the OPAT program. With the exception of patients receiving oral linezolid, treatment for all patients receiving OPAT included at least 1 parenteral antibiotic. Patients receiving OPAT had orders for weekly laboratory evaluations. All patients receiving OPAT were logged in the OPAT database, a prospective database maintained by a single administrative assistant (KSM). Data elements collected included demographic information, dates of treatment, site and/or type of infection, culture results, antimicrobials administered (including both intravenous and oral medication and subsequent medications if treatment was changed during therapy), and antimicrobial-induced complications, such as rash, renal injury, liver injury, neutropenia, and thrombocytopenia. Antimicrobial therapy changes, including medication and duration changes, were determined by the patient's primary infectious disease physician. At the start and end of a course of therapy for each patient, the OPAT medical director (SBN) reviewed all medical charts and laboratory reports, verified database entries, and documented adverse drug reactions.

We retrospectively identified all patients receiving OPAT who began their therapy from September 1, 2012, through December 31, 2013. All patients receiving OPAT who had at least 1 differential CBC were included in the analysis. This study was approved by the Partners Human Research Committee.

Definitions of eosinophilia and HSRs

Consistent with literature-reported definitions, we defined eosinophilia as any AEC of greater than or equal to 500/mL and hypereosinophilia as any AEC of greater than or equal to 1500/mL.[20,24]

All rashes were seen by a medical professional and documented as potentially related to antibiotic therapy. Renal injury was defined as a creatinine level increase of at least 0.5 mg/dL or 50% above baseline creatinine levels. Liver injury was defined as a new alanine aminotransferase level of greater than 100 U/L. We defined onset of eosinophilia as 5 days before the CBC demonstrating eosinophilia and considered an HSR to be any documented rash, renal injury, and/or liver injury occurring after defined onset of eosinophilia. This time frame was chosen based on both the infrequency of OPAT laboratory evaluations and the slow, delayed nature of these HSRs. We conducted a sensitivity analysis using 2 days (rather than 5 days) before the documented date of eosinophilia to determine whether our conclusions were sensitive to this definition. To assess whether any patients had DRESS syndrome, we identified patients with eosinophilia either before or concurrent with rash and either liver or kidney injury within a 3-day time period and subsequently manually reviewed cases using established criteria for "possible DRESS syndrome" and "probable DRESS syndrome."[10,25]

Statistical analysis

Descriptive data were displayed as frequencies or medians with interquartile ranges (IQRs). Exact (Clopper-Pearson) 95% confidence limits for frequencies were calculated from the binomial distribution. Comparisons of variables (eg, diagnoses and organisms) between groups (with or without eosinophilia or with or without HSRs) used the Fisher exact test or Wilcoxon rank sum test, as appropriate.

We considered "initial antibiotics" as those begun during the initial 4 days of antimicrobial treatment. When applicable, specific antimicrobials were grouped into common drug classes (eg, penicillins and cephalosporins). For reporting the proportion of patients using an antibiotic, because exposure in the eosinophilia group was only until the detection of eosinophilia, we normalized follow-up exposure in the noneosinophilia (control) group to have the same time distribution. To do this, for each patient with eosinophilia, we randomly selected patients without eosinophilia and truncated their follow-up time to match that of the case. We randomly selected either 2 or 3 control subjects per patient with eosinophilia without replacement, so that each control subject in the total control population was used exactly once.

For assessing the effect of baseline variables and drug exposures on eosinophilia and HSR onset, we used multivariate Cox proportional hazards models, including time-varying antibiotic treatment indicators (and a time-varying eosinophilia onset indicator for HSRs). Because of the large number of antibiotic classes, we used a backward procedure to construct the multivariate proportional hazards model. The model always included age and sex. Drugs used by less than 1% of patients at any time during follow-up and those with univariate P values of less than .50 were not considered for the multivariate model. Both univariate and multivariate (adjusted for age, sex, and other antibiotics) hazard ratios (HRs) were assessed. Among patients with eosinophilia, we assessed the association of hypereosinophilia with HSRs by using the Fisher exact test for a 2×2 contingency table. Two-tailed P values of less than .05 were considered statistically significant. Statistical analyses were performed with SAS 9.4 software (SAS Institute, Cary, NC).

RESULTS

Patients' characteristics

Among the 827 patients beginning therapy from September 1, 2012, through December 31, 2013, 824 (>99%) had at least 1 differential complete blood count during their OPAT treatment and were included in the analysis. Patients had a median age of 60 years (IQR, 48-71 years), were 60% male, and had a median duration of therapy of 41 days (IQR, 31-45 days); the majority of patients (515/824 [63%]) initiated therapy on a single antimicrobial agent (Table I). The most commonly treated infections were orthopedic infections (n = 464) and bacteremia (n = 161). Most treated organisms were gram positive (n = 641). The most commonly used antibiotics at any time during the entire course of OPAT treatment included cephalosporins (46%), vancomycin (40%), and penicillins (27%, see Table E1 in this article's Online Repository at www.jacionline.org).

Eosinophilia

Eosinophilia was present in 210 (25%) of 824 patients during their course of treatment, with a median peak AEC of 726/mL (IQR, 594-990/mL; range, 500-8610/mL). Median days of therapy until onset of eosinophilia was 15 (IQR, 8-22 days). Patients with eosinophilia were more likely to be older (64 vs 59 years, $P = .0002$) and discharged to a skilled nursing facility instead of home (51% vs 39%, $P = .003$; Table I).

Use of vancomycin, penicillin, rifampin, and linezolid was associated with a significantly higher hazard of having eosinophilia (Table II). Cephalosporins and flouroquinolones were not associated with increased risk of eosinophilia. Use of