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Effect of Omalizumab on Blood Basophil Counts in Patients with Chronic Idiopathic/Spontaneous Urticaria

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Abbreviations: APC, allophycocyanin; CIU, chronic idiopathic urticaria; CSU, chronic spontaneous urticaria; FITC, fluorescein isothiocyanate; IgE, immunoglobulin E; ISS, itch severity score; PerCP, peridinin chlorophyll protein; s.c., subcutaneous; SD, standard deviation

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TO THE EDITOR

Basophils are believed to play an important role in the pathophysiology of chronic idiopathic/spontaneous urticaria (CIU/CSU) (Vonakis and Saini, 2008). Notably, basopenia has been reported in patients with CIU/CSU (Rorsman, 1961) and is postulated to be the result of migration of basophils from the circulation into the skin (Caproni et al., 2005; Ito et al., 2011; Ying et al., 2002). Consistent with this hypothesis, the degree of basopenia has been shown to correlate with disease severity (Grattan et al., 2003) and improves during times of remission (Eckman et al., 2008; Kern and Lichtenstein, 1976). It is theorized that binding of free IgE by omalizumab, a humanized monoclonal antibody against IgE, may influence the behavior of basophils and mast cells via down-regulation of the high-affinity receptor (FcεRI). To evaluate the effect of omalizumab on circulating basophils in CIU/CSU, we conducted a post hoc analysis of randomized clinical trial data examining changes in blood basophil counts in relation to treatment.

Patient data were obtained from three pivotal trials conducted to evaluate the safety and efficacy of omalizumab in patients with CIU/CSU: ASTERIA I (NCT01287117), ASTERIA II (NCT01292473), and GLACIAL (NCT01264939). Written informed consent for participation in the trials was obtained from all patients or their parent or legal guardian, and study protocols were developed in accordance with the principles of the Declaration of Helsinki and approved by the institutional review board or ethics committee at each center. Detailed information regarding these studies has been previously reported (Kaplan et al., 2013; Maurer et al., 2013; Saini et al., 2015).

Patients received subcutaneous omalizumab (75 mg, 150 mg, or 300 mg in ASTERIA I and ASTERIA II; 300 mg in GLACIAL) or placebo every 4 weeks for 12 (ASTERIA II) or 24

(ASTERIA I, GLACIAL) weeks with a 16-week follow-up period. Blood samples for basophil analyses were collected at baseline and every 12 weeks. The presence of blood basophils were quantified using two different methods: whole blood histamine assay and basophil percentage by flow cytometry. Basophils are highly enriched for histamine content relative to plasma or other cellular components of blood. Evidence suggests that the cell-free fraction of histamine is minimal compared with the cell fraction in patients with CIU/CSU (Cho et al., 2013), and thus the measurement of histamine in whole blood lysate correlates closely with basophil levels in the blood (Sabroe et al., 1998; Siraganian, 1974; Siraganian, 1975). Histamine concentrations (measured in lysates only for patients participating in US-based sites) were determined using the method described by Siraganian et al. (Siraganian, 1974; Siraganian, 1975). Flow cytometric assessment of basophils was conducted using samples of sodium heparin anticoagulated peripheral blood. Basophils were identified through gating $CD123^{+}/HLA^{-}DR^{-}/CD303^{-}$ cells.

Overall, the three pivotal trials included a total of 766 patients; 586 received omalizumab and 180 received placebo. The histamine analysis included data from 578 patients (omalizumab, 440; placebo, 138). The basophil percentage by flow cytometry analysis included data from 608 patients (omalizumab, 469; placebo, 139). Baseline demographic and clinical characteristics were similar across studies and treatment groups (Supplementary Table S1, online).

Mean ± SD histamine concentrations were generally similar across treatment groups at baseline (Supplementary Table S2, online). Changes from baseline in histamine concentration are depicted in Figure 1a. The mean changes from baseline in histamine were greater in the omalizumab 300 mg group versus placebo for all three trials at Weeks 12 and 24. Although this difference was not always statistically significant in individual trials, the difference was significant at Week 12 when data from all 3 trials were pooled (omalizumab 300 mg, 4.38,

versus placebo, 0.54; $P < 0.001$). Changes in histamine concentration for the lower dose omalizumab cohorts were less consistent and not statistically significant.

Mean ± SD basophil percentages were generally similar across treatment groups at baseline (Supplementary Table S3, online). Changes from baseline in blood basophil percentage are shown in Figure 1b. As observed for histamine concentration, the mean change in basophil percentage was higher in the omalizumab 300 mg group versus placebo for all three trials at Weeks 12 and 24. Although this difference was not always statistically significant in individual trials, the difference was significant at Week 12 (omalizumab 300 mg, 0.16, versus placebo, 0.03; $P < 0.001$) and at Week 24 (omalizumab 300 mg, 0.19, versus placebo, 0.08; $P = 0.018$) when data was pooled across trials. A similar trend of increased basophil percentage at Week 12 was observed for the 75 mg group (omalizumab 75 mg, 0.08; $P = 0.072$) and the 150 mg group (omalizumab 150 mg, 0.10; $P = 0.039$). Across all three trials, histamine concentrations correlated well with basophil percentages ($r = 0.614$, $P < 0.001$ at baseline and $r = 0.664$, $P < 0.001$ at Week 12; Figure 2).

Among the subset of patients from the pivotal trials included in this post hoc analysis, we observed improvements in weekly itch severity score (ISS) that paralleled the improvements in blood basophil numbers (Figure 1c). Changes in clinical efficacy, as measured by the weekly ISS, correlated weakly with changes in histamine concentration ($r = -0.2139$; $P \leq 0.001$; n = 582) as well as changes in basophil percentage ($r = -0.1486$; $P \leq 0.001$; n = 637).

To our knowledge, this is the first report to prospectively measure basophil presence in circulation relative to clinical measures of CIU/CSU activity, and also the first to examine basophil counts on a large scale within an interventional study. Our analysis of data from the pivotal trials of omalizumab for CIU/CSU showed that circulating blood basophils increased in

response to treatment with omalizumab 300 mg. Parallel improvements in disease severity, as measured by the weekly ISS, were observed across all treatment groups, with the omalizumab 300 mg group demonstrating the greatest clinical benefit. Correlations between weekly ISS and blood basophils measures were weak but significant, suggesting a possible relationship. Taken together, our data suggest that the clinical improvement observed with omalizumab treatment may be related to its effect on basophils.

This analysis is subject to the same limitations of any post hoc analysis of clinical trial data. Whole blood histamine concentrations and flow cytometry data were available for only a subset of patients, thus power to detect smaller changes in these measures was limited. While statistical significance was not achieved at every individual time point, the trends observed were consistent between trials as well as between the two methods used to assess basophils, supportive of an overall treatment-related effect.

In summary, our findings lend further evidence to the hypothesis that basophils play an important role in pathobiology of CIU/CSU. Future investigation is needed to determine whether circulating basophils could serve as a potential useful biomarker for clinical response to omalizumab in patients with CIU/CSU.

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The pivotal trials (ASTERIA I, ASTERIA II, and GLACIAL) were designed and funded by Genentech, Inc., South San Francisco, CA and Novartis Pharma AG, Basel, Switzerland. Medical writing support for this manuscript was funded by Genentech, Inc. and Novartis Pharmaceuticals Corporation.

CONFLICT OF INTEREST

SSS has received research support from AstraZeneca, Genentech, Inc., the National Institutes of Health, and Novartis and has served as a consultant to Array, Genentech, Inc., Kendle, MedImmune, Novartis, Pharmacyclics, and Teva. TAO, BT, KR, and HC are all employees of Genentech, Inc. and receive stock options from Roche. HNH is a paid consultant to Genentech, Inc. PMS and J-PC state no conflict of interest. AL is an employee of LabCorp Clinical Trials, which received payment for performing the flow cytometry assay described in this paper.

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FIGURE LEGENDS

Figure 1. Effects of omalizumab on laboratory and clinical parameters. Change from baseline in (a) mean whole blood histamine concentration (ng/ml), in (b) mean blood basophil percentage (by flow cytometry), and in (c) mean weekly itch severity score in a subset of patients enrolled in ASTERIA I, ASTERIA II, and GLACIAL. *$P < 0.05$ versus placebo.