**A) Sub-analysis to determine the effect of including patients who received a PPI other than esomeprazole on outcome of PPI therapy for esophageal eosinophilia**

Not all patients included in the analysis received esomeprazole: 3 children were treated with lansoprazole (doses: 1.71 mg/kg, PPI-nonresponsive EoE; 1.55 mg/kg, complete PPI-REE; and 2.15 mg/kg/day, PPI-REE) and one child was treated with omeprazole (1.69 mg/kg/day, complete PPI-REE). Due to known differences in pharmacokinetics / pharmacogenetics and molecular weights between different PPIs, equal weight doses of different PPIs have unequal efficacies. Kirchheiner, et al.1 empirically derived equal efficacy doses for different PPIs using omeprazole equivalency (OE) as reference and time that gastric pH remains >4 as efficacy benchmark, however our data, and data from others, suggests that PPI efficacy for esophageal eosinophilia is not a function of acid reduction but rather is consistent with a mechanism proposed by Chang, et al.2 in which omeprazole was found to reduce Th2 cytokine stimulated eotaxin-3 expression in EoE esophageal squamous cell lines. Since it is unlikely that the two mechanisms will have similar dose-response profiles, we decided not to correct PPI dosages to omeprazole equivalency for the current analysis. To determine if PPI-REE outcome was influenced by inclusion of patients who received lansoprazole and omeprazole, we ran a sub-binary logistic regression analysis of just the patients who received esomeprazole (dominant genetic model for CYP2C19\*17 GOF or rs1059513 with race, gender, age, and PPI dose included as covariates). We found that exclusion of patients who received a PPI other than esomeprazole did not significantly influence the results of either the *CYP2C19* or *STAT6* analyses (Table S3).

**Table S3: Sub-analysis of patients who received esomeprazole therapy for esophageal eosinophilia**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Selection** | **Cohort** | **Predictor** | **PPI-REE OR** | **p-value** | **Complete PPI-REE OR** | **p-value** |
| All | pH | GOF | 0.12[0.02,0.67] | 0.016 | 0.15[0.03,0.94] | 0.043 |
| Esomeprazole only | pH | GOF | 0.12[0.02,0.67] | 0.016 | 0.15[0.03,0.94] | 0.043 |
| All | IQR | GOF | 0.13[0.02,0.83] | 0.031 | 0.28[0.04,1.72] | 0.168 |
| Esomeprazole only | IQR | GOF | 0.13[0.02,0.83] | 0.032 | 0.29[0.05,1.77] | 0.179 |
| All | Full | GOF | 0.47[0.17,1.29] | 0.143 | 0.55[0.19,1.59] | 0.270 |
| Esomeprazole only | Full | GOF | 0.47[0.17,1.28] | 0.140 | 0.56[0.19,1.61] | 0.279 |
| All | Full | rs1059513 | 6.16[1.44,26.35] | 0.014 | 7.02[1.98,24.9] | 0.003 |
| Esomeprazole only | Full | rs1059513 | 6.15[1.43,26.35] | 0.014 | 7.03[1.97,25.04] | 0.003 |

**B) Sub-analysis to determine the effect of treatment duration** **on outcome of PPI therapy for esophageal eosinophilia**

The target duration for PPI therapy was 8 weeks. Overall the mean(SD) of PPI therapy duration was 10.0(1.4) weeks, with a high of 13.9 and a low of 4.6 weeks. There were three patients who received PPI for less than 8 weeks (4.6 weeks, PPI-nonresponsive EoE; 6.9 weeks, PPI-nonresponsive EoE; and 7.7 weeks, complete PPI-REE). To determine if PPI-REE outcome was influenced by inclusion of patients who received less than 8 weeks of PPI therapy, we performed a sub-binary logistic regression analysis of individuals who received >= 8 weeks of PPI therapy (dominant genetic model for CYP2C19\*17 GOF or rs1059513 with race, gender, age, PPI dose, and PPI type included as covariates). We found that removal of individuals who received less than 8 weeks of PPI therapy improved the association of *CYP2C19* GOF with outcome in the full cohort (Table S4).

**Table S4: Sub-analysis of patients who received >= 8 weeks of esomeprazole therapy for esophageal eosinophilia**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Selection** | **Cohort** | **Predictor** | **PPI-REE OR** | **p-value** | **Complete PPI-REE OR** | **p-value** |
| All | pH | GOF | 0.12[0.02,0.67] | 0.016 | 0.15[0.03,0.94] | 0.043 |
| >= 8 weeks of therapy | pH | GOF | 0.12[0.02,0.67] | 0.016 | 0.15[0.03,0.94] | 0.043 |
| All | IQR | GOF | 0.13[0.02,0.83] | 0.031 | 0.28[0.04,1.72] | 0.168 |
| >= 8 weeks of therapy | IQR | GOF | 0.13[0.02,0.83] | 0.031 | 0.28[0.04,1.72] | 0.168 |
| All | Full | GOF | 0.47[0.17,1.29] | 0.143 | 0.55[0.19,1.59] | 0.270 |
| >= 8 weeks of therapy | Full | GOF | 0.36[0.13,1.03] | 0.057 | 0.44[0.14,1.32] | 0.142 |
| All | Full | rs1059513 | 6.16[1.44,26.35] | 0.014 | 7.02[1.98,24.9] | 0.003 |
| >= 8 weeks of therapy | Full | rs1059513 | 5.3[1.22,23.04] | 0.026 | 6.29[1.74,22.67] | 0.005 |

**C) Sub-analysis to determine the effect of PPI dosages at or below 1 mg/kg/day on outcome of PPI therapy for esophageal eosinophilia**

The target dosage for the study was 2 mg/kg/day. This target was successfully implemented for 87 patients to a maximum dose of 80 mg/day (maximum adult dose). Variation in the dose range in these patients was due to either their weight exceeding 40 kg or the limited granularity of available esomeprazole formulations (20 mg and 40 mg). Five patients inadvertently received low dose PPI due to a misunderstanding in how to take the medication. Two of them received < 1 mg/kg/day and three received ~1 mg/kg/day, 0,96, 1.12 and 1.18 mg/kg/day. One of these patients was PPI-REE and four were PPI-nonresponsive EoE. The whole population, including patients who received ≤1 mg/kg/day, constitutes the Intention to Treat population. Therefore, all patients regardless of dose were included in the analysis. Dose variability was corrected for by including dose (mg/kg/day) as a covariate in all binary logistic regression models. To determine if PPI-REE outcome was influenced by inclusion of the five patients who received ≤1mg/kg/day, we performed a sub-binary logistic regression analysis of patients receiving > 1 mg/kg/day (dominant genetic model for CYP2C19\*17 GOF or rs1059513 with race, gender, age, PPI dose, and PPI type included as covariates). We found that removal of patients who received ≤1mg/kg/day of PPI did not significantly influence the association between *CYP2C19* or *STAT6* SNP and outcome (Table S5).

**Table S5: Sub-analysis of patients who received > 1 mg/kg/day of esomeprazole therapy for esophageal eosinophilia**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Selection** | **Cohort** | **Predictor** | **PPI-REE OR** | **p-value** | **Complete PPI-REE OR** | **p-value** |
| All | pH | GOF | 0.12[0.02,0.67] | 0.016 | 0.15[0.03,0.94] | 0.043 |
| >= 1 mg/kg/day | pH | GOF | 0.12[0.02,0.67] | 0.016 | 0.15[0.03,0.94] | 0.043 |
| All | IQR | GOF | 0.13[0.02,0.83] | 0.031 | 0.28[0.04,1.72] | 0.168 |
| >= 1 mg/kg/day | IQR | GOF | 0.13[0.02,0.83] | 0.031 | 0.28[0.04,1.72] | 0.168 |
| All | Full | GOF | 0.47[0.17,1.29] | 0.143 | 0.55[0.19,1.59] | 0.270 |
| >= 1 mg/kg/day | Full | GOF | 0.43[0.15,1.21] | 0.109 | 0.48[0.16,1.42] | 0.185 |
| All | Full | rs1059513 | 6.16[1.44,26.35] | 0.014 | 7.02[1.98,24.9] | 0.003 |
| >= 1 mg/kg/day | Full | rs1059513 | 6.04[1.37,26.56] | 0.017 | 6.5[1.82,23.15] | 0.004 |

**References**

1. Kirchheiner J, Glatt S, Fuhr U, et al. Relative potency of proton-pump inhibitors-comparison of effects on intragastric pH. *Eur J Clin Pharmacol.* 2009;65(1):19-31.

2. Cheng E, Zhang X, Huo X, et al. Omeprazole blocks eotaxin-3 expression by oesophageal squamous cells from patients with eosinophilic oesophagitis and GORD. *Gut.* 2013;62(6):824-832.