

# Derivation of a prototype asthma attack risk scale centred on blood eosinophils and exhaled nitric oxide

S Couillard, A Laugerud, M Jabeen, S Ramakrishnan, J Melhorn, TSC Hinks, I D Pavord

**RATIONALE:** Reduction of the risk of asthma attacks is a major goal of clinical management.

**OBJECTIVE:** To develop a risk scale to predict asthma attacks based on the blood eosinophil count and exhaled nitric oxide.

**METHODS:** Trial-level data were extracted from the Novel START, CAPTAIN, Benralizumab phase 2b, PATHWAY, STRATOS 1-2, QUEST and DREAM trials. Attack rates for control arm patients ( $n=3051$ ) were stratified by blood eosinophils and exhaled nitric oxide. Aggregate frequency-weighted biomarker-stratified rate ratios were calculated and applied to reference GINA treatment step attack rates derived from 222,817 patients. Other parameters included were a recent asthma attack history ( $\leq 1$  year),  $\geq 2$  concurrent clinical risk factors\*, and treatment step. We validated the scale by comparing the frequency-weighted predicted versus observed biomarker-stratified asthma attack rates in the derivation trials.

**RESULTS:** Biomarker-stratified asthma attack rate ratios were 0.65 in the lowest type 2 biomarker combination group and 2.29 in the highest. A previous asthma attack and/or having concurrent risk factors independently increased rates 2.8- and/or 1.3-fold, respectively. Predicted annual attack rates ranged from 0.06 in the lowest biomarker step 1&2 patients to 2.6 in the highest biomarker step 5 patients. The resultant scale is shown in Figure 1. There was close agreement between frequency-weighted observed and predicted asthma attack rates: the intraclass correlation coefficient [95%CI] was 0.83 [0.78–0.86], the weighted least squares regression equation was  $y=0.94x - 0.08$  (slope [0.92–0.96], constant [-0.09– -0.07]) with  $R^2 = 0.79$ , and the Bland-Altman fixed bias estimate was -0.08 [-0.58–0.41],

**CONCLUSION:** A prototype scale based on biomarkers of type 2 inflammation shows feasibility and potential to predict asthma attacks which may be prevented by treatment.

**FIGURE 1. Prototype Oxford Asthma Attack Risk Scale (ORACLE).** Numbers in each cell are predicted annual asthma attack rates for patients over the age of 12 if treatment is not changed. Blood eosinophil count is contemporaneous or the highest result in last 12 months; exhaled nitric oxide level is contemporaneous. \*Risk factors are defined by GINA: poor symptom control, low lung function, non-adherence, reliever over-use, previous intubation/critical asthma attack, selected comorbidities, environmental exposures.

Word count: 346/350

**Yes**

**2 or more clinical risk factors\*?**

Yes

0.98	1.32	2.60
0.75	1.00	1.28
0.74	0.93	1.28
0.40	0.54	1.06
0.31	0.41	0.52
0.30	0.38	0.52
0.33	0.44	0.88
0.25	0.34	0.43
0.25	0.31	0.43
0.30	0.41	0.80
0.23	0.31	0.39
0.23	0.28	0.39
< 0.15	0.15-<0.30	≥ 0.30

**Blood eosinophil count (cells  $\times 10^9/L$ )**