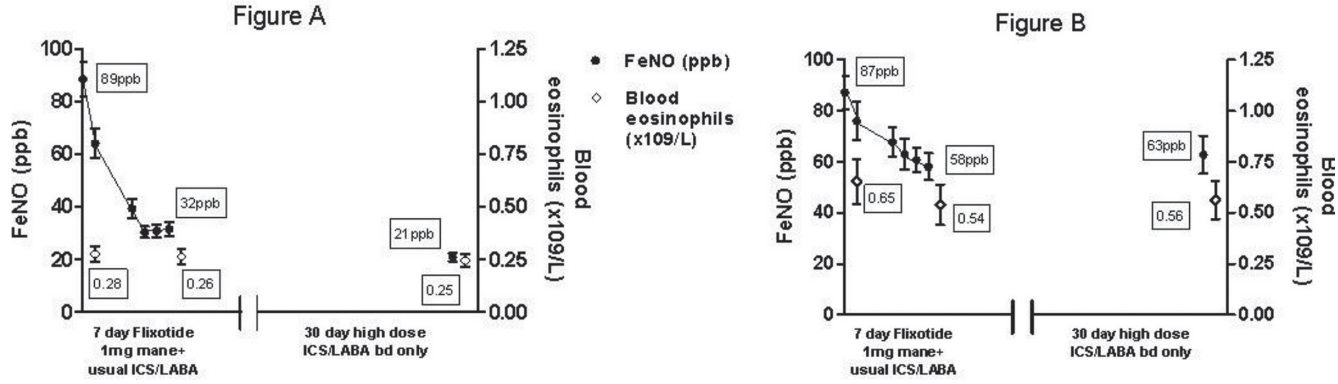

Abstract S2 Figure 1

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S3 THE UK'S LARGEST SEVERE ASTHMA MULTIDISCIPLINARY TEAM MEETING; EXPERIENCE FROM THE FIRST 18 MONTHS

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Background Severe asthma comprises 5% of all asthma, but over 50% of the asthma healthcare burden. With multi-disciplinary team (MDT) working there is potential to improve patient outcomes and reduce healthcare costs. In 2013 NHS England produced service specifications for severe asthma aiming to develop a limited number of high volume specialist centres. In the North West we have developed a networked approach to specialised severe asthma services; the first Operation Delivery Network for a chronic disease. Representatives from 11 NHS Trusts and a central hub undertake a monthly virtual MDT meeting, with physicians, nurses, physiotherapists, clinical psychologists, speech and language therapists, allergists, pathologists and radiologists represented. All patients being considered for specialised treatments undergo MDT discussion for consensus approval of treatment.
Aim To summarise the experience and case-mix encountered during the first 18 months of operation of our regional virtual severe asthma MDT
Methods We reviewed all cases discussed at the MDT between January 2015 and June 2016. Cases were submitted online via nhs.net accounts, and data entered into a central database managed by two MDT coordinators for MDT discussion.
Results During this period 17 meetings were held, with 208 case-submissions representing 185 patients, mean (SD) 12 (7) discussions per meeting. Indications for case submission included proposals for use of omalizumab, bronchial thermoplasty (BT), and steroid-sparing therapies, and for the discussion of patients with complex clinical issues, often managed across multiple sites. Omalizumab was approved in 81% of cases submitted, and BT in 39%, with more of the latter requiring multiple discussions (30% versus 2%) The most common reasons for non-approval of omalizumab were insufficient steroid requirement, poor adherence, and lack of allergy to a perennial allergen. Thermoplasty was not approved or listed for re-discussion for a variety of reasons, including 10 (43%) that required further investigation.
Conclusion We describe our early experience of a multi-site virtual severe asthma MDT meeting facilitating expert care across a wide geographical area. This ensures governance in the use of novel and expensive severe asthma therapies, strengthens regional collaborations and ultimately aims to provide better patient care.

S4 IMPLICATIONS OF GUIDANCE IN SCOTLAND ON ELIGIBILITY FOR TREATMENT WITH MEPOLIZUMAB AND OMALIZUMAB – AN IDEAL STUDY ANALYSIS

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Rationale Severe asthma is a heterogeneous disease in which patients have diverse clinical characteristics and biomarkers, like eosinophils and IgE. It is important to understand their relationship in a severe asthma population. The IDEAL (Identification and Description of Severe Asthma Patients in a Cross-Sectional Study) study aimed to identify the proportion of patients with severe asthma who could be eligible for an anti IL-5 (mepolizumab) or anti-IgE (omalizumab) directed treatment, and those who may be eligible for either therapy.
Methods IDEAL, an observational study included subjects aged ≥12 years with severe asthma defined according to ATS/ERS guidelines by treatment with high-dose ICS plus additional controller(s) for ≥12 months. Assessments included spirometry, a blood sample, and symptom/burden of illness questionnaires. Eligibility to mepolizumab and omalizumab were defined according to SMC advice (2016) and NICE MTA guidance (2013), which has been adopted in Scotland, respectively. Mepolizumab eligibility is defined as per SMC advice: patients who have eosinophils of at least 150 cells per microlitre (0.15 x 109/L) at initiation of treatment and have had at least four asthma exacerbations in the preceding year or are receiving maintenance treatment with oral corticosteroids. Omalizumab eligibility (NICE MTA guidance) is defined as evidence of severe persistent allergic asthma and need for continuous or frequent treatment with oral corticosteroids

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(defined as 4 or more courses in the previous year), and meeting bodyweight and IgE criteria for omalizumab treatment.
Results 748 subjects with severe asthma were enrolled in the study of which 670 met analysis criteria. After exclusion of subjects currently treated with omalizumab (n = 168), 502 subjects were included in this post-hoc analysis (mean age = 50.9 years; 62% female). 60 subjects (12% [95% Exact CI: 9.2–15.1%]) were eligible for mepolizumab (SMC advice) and 16 (3.2% [1.8–5.1]) were eligible for omalizumab (NICE MTA guidance). Among the 60 mepolizumab eligible subjects, 10 (16.7% [8.3–28.5%]) were also eligible for omalizumab.
Conclusions This is the first cross-sectional study providing estimation of the proportion of severe asthma patients eligible for biologic therapy in accordance with Scottish guidance, indicating 12% mepolizumab-eligible and 3.2% omalizumab-eligible patients with limited overlap.
Funding GSK; 201722

S5 VITAMIN D FOR THE MANAGEMENT OF ASTHMA: COCHRANE SYSTEMATIC REVIEW AND META-ANALYSIS

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Introduction and objectives Several clinical trials of vitamin D to prevent asthma exacerbation and improve asthma control have been conducted in children and adults, but a meta-analysis restricted to double-blind randomised placebo-controlled trials of this intervention is lacking. We conducted a Cochrane systematic review and meta-analysis to evaluate the efficacy of administration of vitamin D in reducing asthma exacerbations treated with systemic corticosteroids (primary outcome) and improving asthma symptom control.
Methods Standard Cochrane collaboration procedures were followed. Double-blind randomised placebo-controlled trials of vitamin D in children and adults with asthma evaluating exacerbation risk and/or asthma symptom control were included.
Results Seven trials involving a total of 435 children and two trials involving a total of 658 adults were included in the primary analysis. Administration of vitamin D reduced the rate of exacerbations requiring systemic corticosteroids (Rate Ratio 0.63, 95% CI: 0.45 to 0.88; 680 participants; 3 studies; high quality evidence), and decreased the risk of having at least one exacerbation requiring an emergency department visit and/or hospitalisation (Odds Ratio [OR] 0.39, 95% CI: 0.19 to 0.78; number needed to treat for one additional person to experience a beneficial outcome (NNTB), 27; 963 participants; 7 studies; high quality evidence). There was no effect of vitamin D on % predicted forced expiratory volume in one second (Mean Difference [MD] 0.48, 95% CI: −0.93 to 1.89; 387 participants; 4 studies; high quality evidence) or Asthma Control Test scores (MD −0.08, 95% CI: −0.70 to 0.54; participants = 713; studies = 3; high quality evidence). Administration of vitamin D did not influence the risk of serious adverse events (OR 1.01, 95% CI: 0.54 to 1.89; 879 participants; 5 studies; moderate quality evidence). No participant in any included trial suffered a fatal asthma exacerbation.
Conclusions Meta-analysis of a modest number of trials in patients with predominantly mild to moderate asthma suggests that vitamin D is likely to reduce the risk of severe asthma exacerbation and reduce health care use.

Lung Cancer Biology and Mechanisms

S6 MMP12 AND LMO7, TWO KEY PLAYERS ON OPPOSITE SIDES OF EARLY LUNG SQUAMOUS CELL CARCINOMA DEVELOPMENT

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Background Our laboratory has a unique cohort of patients with pre-invasive lung squamous cell carcinoma (SqCC) lesions, within which there is a clear discrepancy between the prevalence of pre-invasive lesions and the incidence of lung cancer, suggesting that not all pre-invasive lesions progress to cancer. Using gene expression microarrays we identified 1846 genes significantly differentially expressed between progressive and regressive pre-invasive SqCC lesions.

The macrophage metalloelastase MMP12 gene was found to be highly expressed in progressive lesions, and we hypothesised that it plays a role in epithelial-to-mesenchymal transition (EMT). Conversely, the actin binding protein LIM-domain only 7 (LMO7) gene was highly expressed in regressive lesions, and we postulated that it may be protective against EMT due to its role in the maintenance of epithelial architecture.

Initial studies using three SqCC cell lines (A431, H357 and H376) with MMP12-shRNA knockdown showed a significant decrease in migration and invasion compared to non-silencing shRNA controls. LMO7-shRNA knockdown in HBECS was found to significantly increase migration. The aim of this study is to further characterise the function and signalling of MMP12 and LMO7 in lung SqCC development.
Methods Eight-week-old NOD/SCID mice were used for tumorigenesis experiments. Adhesion assays were carried out to assess the roles of MMP12-knockdown or LMO7-overexpression on cell adhesion. Cell signalling mechanisms were assessed using western blotting, qPCR and immunostaining.
Results We observed that MMP12-knockdown decreases tumorigenicity in an immunocompromised mouse model. Both A431- and H357 MMP12-knockdown cells produced significantly smaller tumours compared with non-silencing shRNA cells. We found that MMP12-knockdown decreases cell adhesion, which is currently being further investigated along with effects on integrin signalling pathways. Levels of EMT markers were assessed in MMP12-knockdown and LMO7 overexpressing cells using qPCR, western blotting and immunostaining. Results indicate that higher MMP12 expression is associated with a mesenchymal phenotype, whereas higher LMO7 expression is associated with an epithelial phenotype.
Conclusions Our results suggest that MMP12 is a key driver of migration and invasion in SqCC and its high expression may contribute to EMT, whereas LMO7 is a putative tumour suppressor with a crucial role in maintaining epithelial cell architecture. MMP12 and LMO7 may be potential early stage therapeutic markers for lung cancer.

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