P24 VITAMIN D LEVELS ARE LOW IN SARCOIDOSIS AND CONTRIBUTE TO ABNORMAL MONOCYTE ACTIVITY

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Introduction Sarcoidosis is a multisystem inflammatory disorder. We showed recently that monocytes from patients with sarcoidosis exhibited reduced IL-10 production, and were less able to suppress T cell proliferation[1]. Vitamin D is reduced in a number of inflammatory and autoimmune disorders and has been shown to influence the activity of immune cells, including monocytes. We had observed reduced Vitamin D levels in our sarcoidosis patients and hypothesised that this may contribute to immunepathology by altering monocyte function.

Methods Forty-six steroid-naïve, non-smoking individuals with histology-confirmed sarcoidosis were recruited from our Sarcoidosis-ILD service at first presentation. Serum calcidiol levels were compared with age and gender matched healthy controls. All donors were sampled between July and mid-October when Vitamin D levels were expected to be maximal. Monocytes were isolated using magnetic bead separation, stimulated with lipopolysaccharide (LPS) and cultured overnight with clinically 'sufficient' (10^{-7} M) or 'deficient' (10^{-8} M) levels of calcitriol. Monocyte function was assessed through cytokine production (by flow cytometry and ELISA) and multinucleate giant cell formation (MGC) (*in vitro* fusion assay).

Results Vitamin D (calcidiol) levels were reduced in sarcoidosis (median 25.35 ng/ml [18.43–45.05]) compared with healthy controls (median 75.3 ng/ml [IQR 52.0–88.1]; $p < 0.01$). For the *in vitro* monocyte studies, calcitriol treatment resulted in adose-dependent (i) increase in monocyte IL-10 production ([IL-10-producing monocytes, as %total monocytes] from a baseline of10.2% [9.4–12.0] to 27.6% [25.6–29.4] when cultured with 'deficient' dose of vitamin D and to 30.8% [28.9–32.6]); p.

Conclusions Vitamin D levels are decreased in sarcoidosis patients at presentation. Monocyte IL-10 production was increased, and pro-TH1 differentiation cytokines were reduced with Vitamin D. Correcting Vitamin D deficiency in sarcoidosis patients may redress abnormal monocyte activity and reduce disease activity.

REFERENCE

1 Crawshaw A *et al*. *Eur J Immunol.* 2014

P25 DISTINCT PRO-INFLAMMATORY GENE EXPRESSION PROFILE IN MONOCYTES FROM SARCOIDOSIS PATIENTS WITH ACTIVE DISEASE

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Introduction Monocytes are potential key cellular players inthe early pathogenesis of sarcoidosis. Having previously identified altered monocyte activity in sarcoidosis,[1] we now examine monocyte whole genome expression profile in order to determine potential processes and pathways involved in the perturbed immune activity of these cells.

Methods Patients with tissue-confirmed sarcoidosis (three high-activity, three low-activity, identified by a predefined clinical activity score)[2] were recruited: gene expression profiles compared with age and gender matched healthy controls. All donors were Caucasian, corticosteroid (and other immunemodulatory treatment) naïvenon-smokers. Monocytes were isolated by CD14-negative magnetic selection within 3 h of venesection, RNA extracted using a proprietary kit and stored at -80°C prior to single batch hybridisation with Illumina HumanHT-12 v4 chips.

Results A total of 3437 genes were differentially expressed in sarcoidosis monocytes compared with controls (adjusted p value of <0.05). Filtering by Log_2 fold change of at least1.5 identified 151 differentially expressed genes among these. Principal component analysis demonstrated clear segregation between sarcoidosis and controls, and between those with high and low activity, with low activity clustering closer to healthy controls. IL-6 was the most significantly upregulated gene (Log_2 FC 4.723 adjusted $p < 0.001$). Other significantly upregulated genes included the pro-inflammatory cytokines IL1A (2.987, 0.001) and IL1B (2.952, 0.001); and the monocyte chemotactic factors CCL20 (4.212, 0.002), CXCL2 (4.057, <0.001) and CCL3 (3.470, 0.003). Gene set enrichment analysis identified gene ontology (GO) gene sets relating to inflammatory andimmune system responses to be amongst the most positively enriched genes in the monocytes from patients with active disease ($p < 0.001$, normalised enrichment score [NES] 2.22 and 2.20 respectively).

Conclusions Sarcoidosis monocytes sarcoidosis have a distinct gene expression profile exhibiting a pro-inflammatory, chemotactic phenotype. IL6 may be implicated in the initiation and maintenance of alveolitis and hypergammaglobulinemia in sarcoidosis and the recent interest in the use of humanised anti-IL-6R antibodies in the treatment of rheumatoid arthritis and other immune mediated disease makes functional characterisation of the role of IL-6 in the pathogenesis of sarcoidosis an exciting prospect.

REFERENCES

1 Crawshaw A *et al*. *Eur J Immunol* 2014
2 Kendrick YR *et al*. *Am J Respir Crit Care Med* 2013;187:A1391

P26 P38 MAPK INHIBITION ENHANCES CORTICOSTEROID EFFECTS IN HUMAN EPITHELIAL CELLS VIA INCREASED GR NUCLEAR LOCALISATION

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Background Phospho-p38 MAPK expression is increased in airway epithelial cells in patients with severe asthma and in COPD patients compared to controls. Increased p38 MAPK activation may lead to reduced corticosteroid responsiveness. We have used a human cell bronchial epithelial cell line to investigate the effects of a p38 MAPK inhibitor in combination with a corticosteroid on inflammatory cytokine stimulation.

Methods The human epithelial cell line 16HBE14o$^-$ was used to determine the effects of dexamethasone (0.1–1000 nM) alone, the p38 MAPK inhibitor BIRB-796 (1–1000 nM) alone and both drugs combined at all concentrations on LPS (1 µg/ml), Poly I:C

(100 μg/ml) or TNFα (10 ng/ml) -induced IL-6, IL-8 and RANTES. 16HBE14o$^-$ cells were treated with BIRB-796 (1–1000 nM) alone and in combination with dexamethasone (0.1 nM) for 30 min and glucocorticoid receptor (GR) nuclear translocation determined by immunofluorescence. The effects of TNFα stimulation on the phosphorylation of p38 and GR (serine 226) in 16HBE14o$^-$ cells were determined by Western blot analysis.

Results Maximum inhibition of dexamethasone and BIRB-796 in combination was significantly greater than either drug alone for LPS and TNFα induced IL-6 and IL-8 and for Poly I:C induced RANTES ($p < 0.05$ all comparisons). BIRB-796 (1000 nM) alone had no effect on GR translocation. BIRB-796 (1000 nM) used in combination with dexamethasone (0.1 nM) significantly increased nuclear GR (76.6% nuclear staining) compared to dexamethasone (0.1 nM) alone (4% nuclear staining). TNFα stimulation increased both p38 and GR serine 226 phosphorylation by 15 min. Pre-incubation with BIRB-796 abolished p38 phosphorylation and reduced GR serine 226 phosphorylation.

Conclusion P38 MAPK inhibition enhances the effect of corticosteroids on inflammatory cytokines in human epithelial cells. This enhancement is due to inhibition of p38 dependent phosphorylation of GR serine 226 which leads to increased nuclear localisation of GR.

Keeping your distance: telemonitoring and telehealth

P27 THE USE OF TELEMONITORING TO ASSIST IN THE EARLY SUPPORTED DISCHARGE FOR PATIENTS ADMITTED WITH AN EXACERBATION OF COPD

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Introduction In 2011 the Whole Systems Demonstrator programme findings showed that, if used correctly, Telehealth can deliver 14% reduction in bed days and an 8% reduction in tariff costs in patients with chronic conditions. However little data is available on using Telehealth to assist in the acute setting of early supported discharge of COPD patients as most previous studies focused on its use to assist the long term case management of these patients.

Methods After training of staff within the COPD early support discharge (ESD) team in Salford (CAST), 17 HomePods were made available for this 12 months pilot starting in 2013. Patients were selected based on their ability to use the technology and on availability of HomePods. Pods were left with patients for 30 days and provided remote real-time monitoring of patients before they were re-deployed again to another patients. During the deployment period, patients were supported by a combination of telephone calls and home visits.

Objectives

- Measure the impact of Telehealth on 30 day readmission rates in this cohort
- Test the impact of new technology on caseload/ work load of CAST
- Test the acceptability of Telehealth on this cohort and on CAST
- Asses impact on ability to selfcare
- Measure patients' satisfaction

Outcomes – 73/285 (25%) patients received this intervention with the CAST team

– 30 day re-admission rates within the intervention group was 3% compared to 8% in the other ESD patients, and 18% within the Respiratory directorate

– Those in the telehealth group accounted for 5% of all home visits and 25% of all phone calls made by CAST

– The capacity of CAST was increased from 15 Cases to 18 cases at any one time (20%)

– Patients' survey showed excellent impact on

- Patients' satisfaction
- Confidence in self care
- Patients acceptability and likeability to Telehealth
- Good suggestions were made by patients for improvement

Conclusions The use of Telehealth in the context of ESD for COPD patients admitted with an exacerbation appears to have favourable effect on relevant outcomes without impact on workload and therefore might me a useful tool to consider.

P28 THE USE OF SMARTPHONE APPLICATION (COPD ASSIST) TO SUPPORT THE IMPLEMENTATION OF LOCAL PRIMARY CARE GUIDELINES ON THE MANAGEMENT OF PATIENTS WITH COPD

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Introduction Smartphone applications (apps) have become increasingly popular and offer us up-to-date access to information "on the go". Many national and international societies, medical journals and healthcare organisations develop their own apps; However using apps on a local level to promote implementation of local COPD guidelines and education has not been previously evaluated.

Methods Funding was provided by Salford's CCG innovation fund. A Smartphone app developing firm was commissioned and a development plan was agreed as follows:

1. Close liaison with the lead respiratory physician throughout the project.
2. A primary care focus group helped develop a Beta version for testing prior to launch.
3. App launched as "COPD Assist"
4. Promotion to primary care clinicians via newsletter articles, press releases, seminars, and the intranet
5. Regular data collection on app downloads to measure usability
6. Users' feedback and suggestions via app reviews
7. App downloads initially restricted to Salford clinicians

Objectives

1. Provide primary care clinicians with access to local guidelines and relevant contact details for COPD services anytime, anywhere.
2. Provide the most up-to-date guidelines
3. Offer clinicians access to educational material including videos (inhaler technique, spirometry, and pulmonary rehabilitation) and the opportunity to share this information with patients.
4. Provide up to date pricing of various inhaled therapies