Refractory Asthma Stratification Programme

April 2016

Breath Deep: Issue 1

Welcome to the first issue of the Refractory Asthma Stratification Programme (RASP-UK) newsletter! We hope we will be able to bring you regular updates on the RASP-UK programme and related subjects through the newsletters. We have reached a significant milestone, with the first patient screenings and randomisations taking place and over the next few months we are looking forward to seeing further patients being recruited.

Inside:

Welcome to the Refractory Asthma Stratification Programme UK Newsletter

by Professor Liam Heaney, Programme Leader

We have finally kicked off the RASP-UK programme (http://www.rasp.org.uk). Thanks to everyone in the consortium for all your help in getting to this stage. We've even managed to engage severe asthma centres in the Republic of Ireland with Professor Richard Costello, through the Inhaler Compliance Assessment programme (a prospective randomised multicentre study to optimise the management of symptomatically uncontrolled asthma patients [INCA-SUN]) http://pi.rcsi.ie/include/pi/users/research_descpopup.asp?grant_id=2085.

So even if there is a 'BREXIT' we will continue to work closely with the EU.....both across the Irish border with INCA-SUN and as we assist with the investigation of some of the exciting findings from the pan-European Unbiased Biomarkers for the Prediction of Respiratory Disease Outcomes (U-BIOPRED) programme in the Study of Mechanisms of action of Omalizumab in Severe Asthma (SoMOSA).

Now the real work begins! We know that the aims of the programme are ambitious in RASP-UK but we have a real opportunity to lead the way in the development of a ground-breaking clinical stratification programme for patients with severe asthma.

We hope that this initiative will also allow us to learn from each other, from best practice in our clinical services and we also have a unique collaboration between academia, the health service and industry.

We all recognise that severe asthma is an umbrella term that defines a heterogeneous clinical problem including comorbid conditions, the understanding of which is further complicated by treatment non-adherence (which is often non-intentional with patients doing their best to take multiple inhaled therapies effectively); we also know that when these issues are effectively identified and addressed, good symptom control can frequently be achieved. However, there are many aspects of the pathophysiology of severe asthma that remain unanswered. Traditionally, we have increased corticosteroid treatment in non-responsive patients in an attempt to get better disease control but it is clear that in some patients their symptoms are not corticosteroid responsive. We have become more conscious over the years that as corticosteroid doses are increased, the side effects become much more of an issue for our patients. Our programme is focussed on identifying patterns of disease, which are unresponsive to steroids and therefore target their use more effectively - moving away from the current 'one size fits all' approach to treatment guidelines.

We see the future of severe asthma management involving treatment optimisation to individual patients fully utilising currently available treatments more efficiently, particularly with corticosteroids by defining an 'optimised' dose, allied with the use of 'add-on' target-specific novel treatments. At present there seems to a "tsunami" of novel treatments aimed at targeting Type-2 cytokine mediated inflammation approaching introduction in the clinic. Understanding where these new treatments will fit into the current management is likely to define our therapeutic journey in the coming years. This new 'era' and our collaborative efforts in this UK clinical research programme will hopefully deliver better management for our patients as well as contribute to the identification of novel targets in this exciting era of stratified medicines in severe asthma.

An Important Notice

from Gabrielle Gainsborough

If you would like to share any relevant news with the consortium, have any suggestions or comments on the RASP-UK programme we would be delighted to hear from you. You may even like to contribute a short article. So please get in touch with Gabrielle Gainsborough at Niche Science & Technology.

gabrielle.gainsborough@niche.org.uk

Work-strand 1
Adherence programme

The Adherence programme is progressing and all sites will soon have access to the kit for fractional exhaled nitric oxide (FeNO) suppression testing. The testing is now very straightforward and the Vitalograph laptops allow seamless 'plug and play' upload and analysis of the FeNO and INCA data through the Vitalograph server. Key observations to date are that the 7-day FeNO suppression testing is predictive of composite biomarker profile (FeNO and blood eosinophil count) at one month and identifies subjects who can be optimised using improved adherence with high dose inhaled steroids and subjects who need treatment escalated. Remember – much of the non-adherence is 'non-intentional' and reflects challenges with inhaler technique or timing which can be optimised using the INCA system and patient feedback.

If you have any queries about the technology or testing, contact Kathy Hetherington at: kjhetherington92@gmail.com

The INCA-SUN study has started in Ireland which will formally examine the role of feedback using the INCA system compared to standard care. This study will additionally explore if the composite biomarker profile being used in the steroid adjustment study predicts those who do better with better adherence with inhaled steroids.

Work-strand 1
Biostratification Study

By Dr Avril Horn, Study Manager

The first patients have now been screened and randomised in the Biostratification study (Work-strand 1). At the time of writing this we have 14 patients randomised from five centres and a further 13 patients in screening. If you have screened your first patients - well done and thanks for all your efforts! You may not yet have started screening or you may be experiencing issues, please let me know if you need help in any way so that we can get the study started at your centre as soon as possible.

Our first key learning has been that the first sites to randomise patients have successfully done so by stressing to potential candidates that the study is designed to optimise their steroid dose and minimise side effects, while maintaining symptom control. We believe this approach has been better received than if we had simply presented the study as a means of reducing their inhaled steroids.

I wanted to highlight a few points about management of the study that may be relevant:

- The RASP-UK website –is now online and copies of all relevant study documents are available through the secure login portal at http://www.rasp.org.uk/
- Electronic case report forms (eCRFs) – the ***demonstration*** database is still open for team members to practise on before entering patient's details into the live database, https://cl2.n3-dendrite.com/csp/raspdev/intellect/login.csp
- Please remember that in the concomitant medication section of the eCRF, combination asthma products should be entered as a separate line entry for each component of the medication, e.g., for Symbicort, please record two lines, one for the budesonide and one for the formeterol. This is critical to the accurate calculation of doses of inhaled steroids and long acting beta-adrenoceptor agonists that patients are taking during the study
- Covance lab kits – if you are planning to screen your patients in groups of two or more patients please remember to order extra lab kits before screening. This is important as Covance need ten working days to resupply these kits
- Study budget – the study budget has been provided to cover all study costs including patients travel expenses

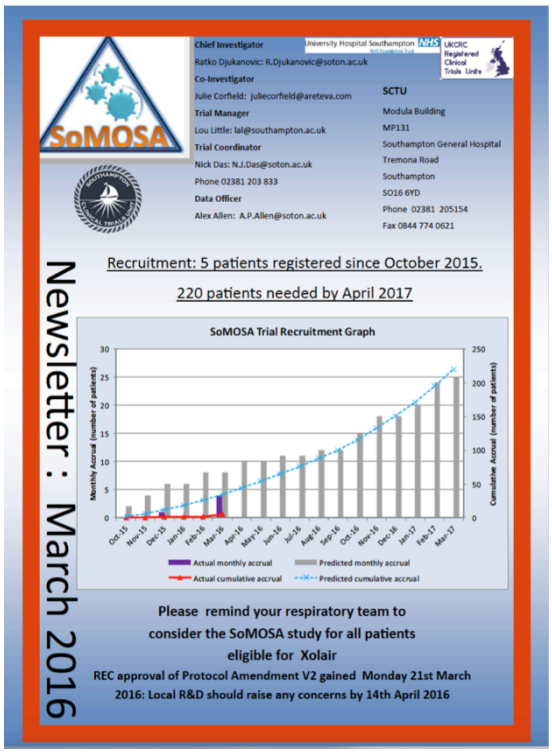
Work-strand 3

The Study of Mechanisms of Action of Omalizumab in Severe Asthma (SoMOSA) – Study Progress

by Professor Ratko Djukanovic, SoMOSA Chief Investigator and Nick Das, SoMOSA Project Manager

SoMOSA has started! The first patient was treated with Xolair in Southampton on 30th December 2015. The second treatment followed in Sheffield. The first steps have been taken for Work-strand 3!

The following sites have been initiated: Southampton, Belfast, Sheffield, Leicester, Oxford, Nottingham, Manchester and Glasgow. Portsmouth will be set up by the end of the month. Many thanks to the Principal Investigators (PIs), study co-ordinators, research nurses, doctors and technicians at each of our sites.



Birmingham, University College London, Guy's & St Thomas', Newcastle and the Royal Brompton are yet to be initiated. The PIs are working hard to remove any outstanding obstacles (which are mainly staffing issues) and are being helped by Alessandra Gaeta from the NOCRI Translational Research Partnership (TRP) team. Alessandra's work in helping with contracts and site initiations has been invaluable, underlining the value of the contribution made by the whole TRP concept.

Work-strand 3

SoMOSA – What have we learned so far?

After study launch, and during site initiation and first screening attempt, several issues have been identified in the protocol itself. These were picked up by people on the ground, working through the eCRF to recruit patients. Many thanks to those who have taken the time to report issues which may have hampered screening and recruitment. For example, because the text was not entirely clear, there was an impression that patients would not be suitable if they had more than four exacerbations in the past year – this is not the case; anyone who has had more than two exacerbations in the past year is eligible and there is no upper limit to exacerbation rates. We also realised that the inclusion criteria based on the dose of inhaled steroids needed to be clarified.

The multiple issues identified led to extensive discussions with PIs and with Novartis. Many thanks to all for their excellent contribution, in particular Liam Heaney, Rekha Chaudhuri, Ian Sabroe and Chris Brightling. A revision of the protocol was submitted via the Integrated Research Application System (IRAS) on 10th March 2016. We do not expect there to be any delay to study progress and will inform you as soon as the changes are approved.

What now?

1. Revised inclusion/exclusion criteria – we will be sending you these in a separate SoMOSA newsletter. Please note that they will not be applicable until ethics approval has been granted. Nevertheless, please read them carefully so that you can identify suitable patients for enrolment as soon as we get the green light from ethics
2. Recording patients' asthma medication – we will also be sending you a list of brand drug names to use when completing the asthma medication. We have considered carefully whether to have pull downs but because there are so many different inhalers this was not practical. Instead, we will ask you to use the brand names of medication as specified in the instructions. This will allow the data analysts in the Southampton Clinical Trials Unit to tabulate all the treatments using their macros
3. We will be sending you our recruitment log
4. Improved communication – we will be organising regular teleconferences for PIs and their coordinators so that we can share information on a regular basis

Many thanks indeed for your continued enthusiasm!

Work-strand 2
Bronchoscopy Study and Work-strand 4 Proof of Concept Clinical Trial – An Update

We have made exciting progress in Work-strands 1 and 3 and are delighted to report that the bronchoscopy protocol and standard operating procedures for work-strand 2 will be submitted for Research Ethics Committee (REC) approval shortly. Currently, nine of our RASP-UK sites are due to take part in the study: Belfast, Birmingham, Brompton, Glasgow Gartnavel and Stobhill, Leicester, Nottingham, Oxford and Manchester. We are aiming to see our first Bronchoscopy patients enrolled in September 2016.
If you have any queries about the technology or testing, contact Kathy Hetherington at: kjhetherington92@gmail.com

In addition, the Work-strand 4 team are working towards submitting the first of the strands proof of concept studies to the REC and Medicines and Healthcare products Regulatory Agency for approval. The first study will be a single centre pilot study (Leicester – Professor Chris Brightling) with the Genkyotex specific small molecule NOX4 inhibitor (GKT137831). We are looking forward to the start of the study, which is due to start in the second quarter of 2016.

RASP UK Events

Thanks to everyone who attended the RASP-UK General Assembly Meeting held on 1st December 2015 at One Drummond Gate, Victoria, London.

This was the first time all consortium members had gathered in one place and it was a great opportunity for the consortium to receive updates from the speakers and each other to discuss the RASP-UK programme. Thanks to the speakers at this meeting who included Liam Heaney, Anthony Rowe, Val Husdon, Courtney Coleman, Richard Costello, Alessandra Gaeta, Avril Horn, Peter Bradding, Ratko Djukanovic and Tim Hardman. The presentation slides are now available on the secure user area of the website.

RASP UK Partner News

Congratulations to Professor Ratko Djukanovic and his research team at Southampton General Hospital and the University of Southampton, who have featured in a news article on the trading webpage '4-traders'. The article outlined the research being undertaken at the University of Southampton by the collaboration between Novartis and the National Institute for Health Research Southampton Respiratory Biomedical Research Unit as part of work-strand 3 of the RASP-UK programme. Professor Djukanovic described the need to find better therapeutic approaches for severe asthma and the work being done to identify biomarkers and help target treatment for maximum benefit from Omalizumab treatment. The article is available to read at the website:
http://www.4-traders.com/NOVARTIS-AG-9364983/news/NOVARTIS-University-of-Southampton-New-trial-to-improve-treatment-for-severe-asthma-patients-22021511/

Newsletters

Please let us know if you would like to share any news with the RASP-UK consortium. Your suggestions or comments on the RASP-UK programme are always welcome!