ADAPT News

The newsletter about alpha-1-antitrypsin deficiency

November 2011 Issue 7

Team update

Rebecca Bray
ADAPT Project Co-ordinator

Hello to old, new and future ADAPT members I am Becky the ADAPT Project Co-ordinator. I have been working on the project for the past 14 years, firstly as administrator and latterly as the co-ordinator. It has been a while since we have produced a newsletter but I hope you find this current newsletter informative and interesting. Professor Stockley and the team would like to thank you all for your continued help, interest and support in the project and I would like to thank everyone who has contributed to this newsletter issue.

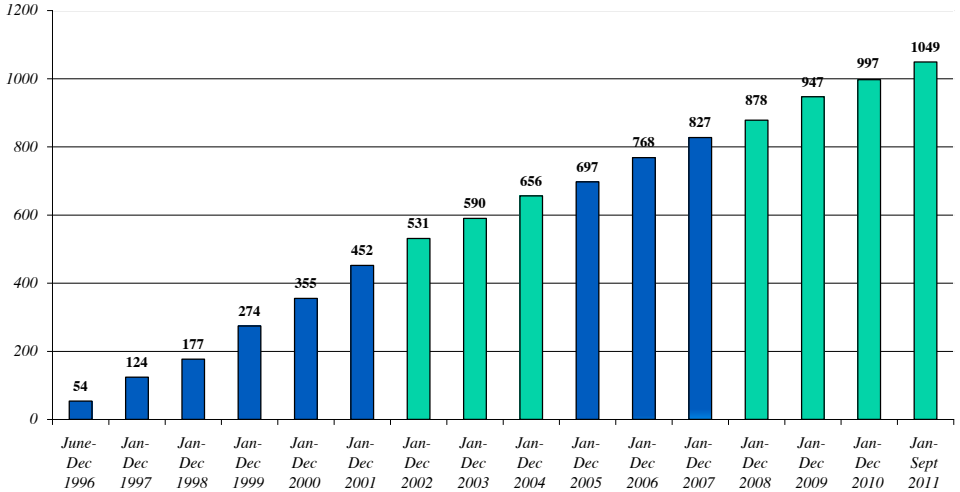
Since our last newsletter we have moved to our new home in the new Queen Elizabeth Hospital Birmingham which is wonderful with only one exception that Anita and I don't have a window in our office to gaze out of and keep an eye on the weather. There have also been changes within the team in that Dr. Richard Carter and Dr. Helen Ward have now left us and gone back onto the hospital rotation.

The team has been working very hard over the last few years with various scientific research and clinical trials. The second phase of the ROCHE trial was completed back in September 2008. At present we are in the middle of the KAMADA inhaled replacement therapy drug trial which is going well and will continue for the next 12 months. There is more information about trials inside as both Anita Pye and Professor Stockley have written very informative articles.

In this issue we have articles from the Alpha-1 UK support group following their annual meeting, Mr. Paul Avison and Mr. Alan Booty on their trial experiences, articles from the team on the progress of the project and information on oxygen and flying and alpha-1-antitrypsin inheritance, which I hope you will all find of interest.

The assessment programme is continuing to run well and we are still recruiting ZZ and other rare variant patients on a monthly basis.

Patients Recruited to ADAPT Assessment Programme - June 1996-Sept 2011



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Research

Clinical Trials

Professor R.A. Stockley

It is essential that robust clinical trials are undertaken to prove that specific treatments work. This is a long drawn out process that costs hundreds of millions of pounds. In the past the most accepted measure of the severity of chronic obstructive pulmonary disease (COPD) has been the forced expired volume of breath in 1 second (the FEV_1). This is a relatively simple test carried out by spirometry and in general relates to the patients symptoms, exercise capacity and quality of life. For these reasons any treatment that improves the FEV_1 or slows its decline is perceived to be beneficial.

Drugs such as the inhaled agents (corticosteroids and bronchodilators) do produce some improvement in FEV_1, exercise and reduce exacerbations (episodes of sudden and short lived deterioration) on average in a group of COPD patients and many relatively short clinical trials (6 months to 3 years) have proven this and these drugs are the mainstay of COPD management.

However, as disease gets worse the FEV_1 continues to fall and treatments are being developed to prevent this and stabilise patients. Clinical trials of such agents are enormously difficult and require large numbers of patients studied over 3-5 years to prove efficacy. This is essentially the problem with alpha-1-antitrypsin deficiency (AATD).

Having AATD increases the likelihood of developing COPD (specifically emphysema) even in non-smokers. It seems logical that replacing the AAT should at least slow the process down. For these reasons Prolastin® was developed in the 1980s. It became apparent that a conventional clinical trial in which some patients received Prolastin® and some received a placebo (injection of fluid without Prolastin®) could not be done to see if it prevented the progression of COPD as measured by the FEV_1. This was for several reasons but specifically because it was prohibitively expensive and because there were insufficient patients diagnosed with AATD.

Because of this the Food and Drug Administration (FDA) in the USA accepted only the logic and demonstration that AAT levels and function could be improved to grant a product licence under "Orphan Drug Status".

However, many countries in Europe and especially the UK did not accept this decision and still required a conventional clinical trial to prove efficacy.

Many observations of patients over the years have provided tantalising evidence of efficacy and the general body of opinion is that Prolastin® (and other forms of AAT) are **probably** effective. But **probably** is not proof. For instance in the large NIH registry patients who received Prolastin® **for at least** 6 months had a mortality rate the same as patients **always on treatment** and this was less than patients who **never** received treatment. In the UK where patients **never receive treatment** the mortality rate is the same as the USA patients **on treatment**.

The NIH registry also showed that if FEV_1 was between 1/3 and 2/3 normal Prolastin® slowed down the decline but not if the FEV_1 was close to normal or worse than 1/3 normal, so many patients with the worst lung function do not qualify for treatment.

ADAPT was established to investigate all of these issues but especially whether a robust clinical trial could be performed to satisfy all countries that Prolastin® worked. The first step was therefore to identify patients, study the disease, monitor its progress and determine the most sensitive way to follow patients. This requires many patients studied over many years especially as it remained clear that it would never be possible to design and deliver a trial based on FEV_1.

We pioneered the research in CT scanning showing that it was the best method to assess the progress of emphysema and that if Prolastin® worked it would not make patients suddenly feel better but would slow down the rate of decline in the lungs.

This now created new problems. Firstly, assessing emphysema gives different results with different scanners so we had to develop methods to ensure that calibration of all scanners could be achieved so that wherever the data was collected it was the same.

Secondly, we had to convince the FDA and European regulators that CT was a robust and important outcome for disease rather than the FEV_1. A task that has taken years until recently.

Thirdly, we had to design a robust study that would provide the answer. However, since we could not be sure that Prolastin® would stop the decline in emphysema but may only slow it down we did not know how many patients we would need to enter the study to prove the difference between Prolastin® and the placebo.

Fourthly, as with all clinical trials it had to be run in more than one country which presented enormous control need for each centre. Finally we had to secure funding for the study.

EXACTLE ran over 3-4 years in 3 countries involving 82 patients and cost in excess of $80million. At the end of the study the results showed that Prolastin® slowed down emphysema progression if the most sensitive analysis was used. This data was not accepted as proof, but rather supportive of efficiency.

We re-analysed the previous Dutch Danish study using our sensitive method and that also showed an effect but they drug used was not Prolastin® and was only given once a month. We combined the 2 studies as this increased the numbers and the combined data provided highly statistically significant data of AAT replacement efficacy but many reviewers of the publication still criticised the data.

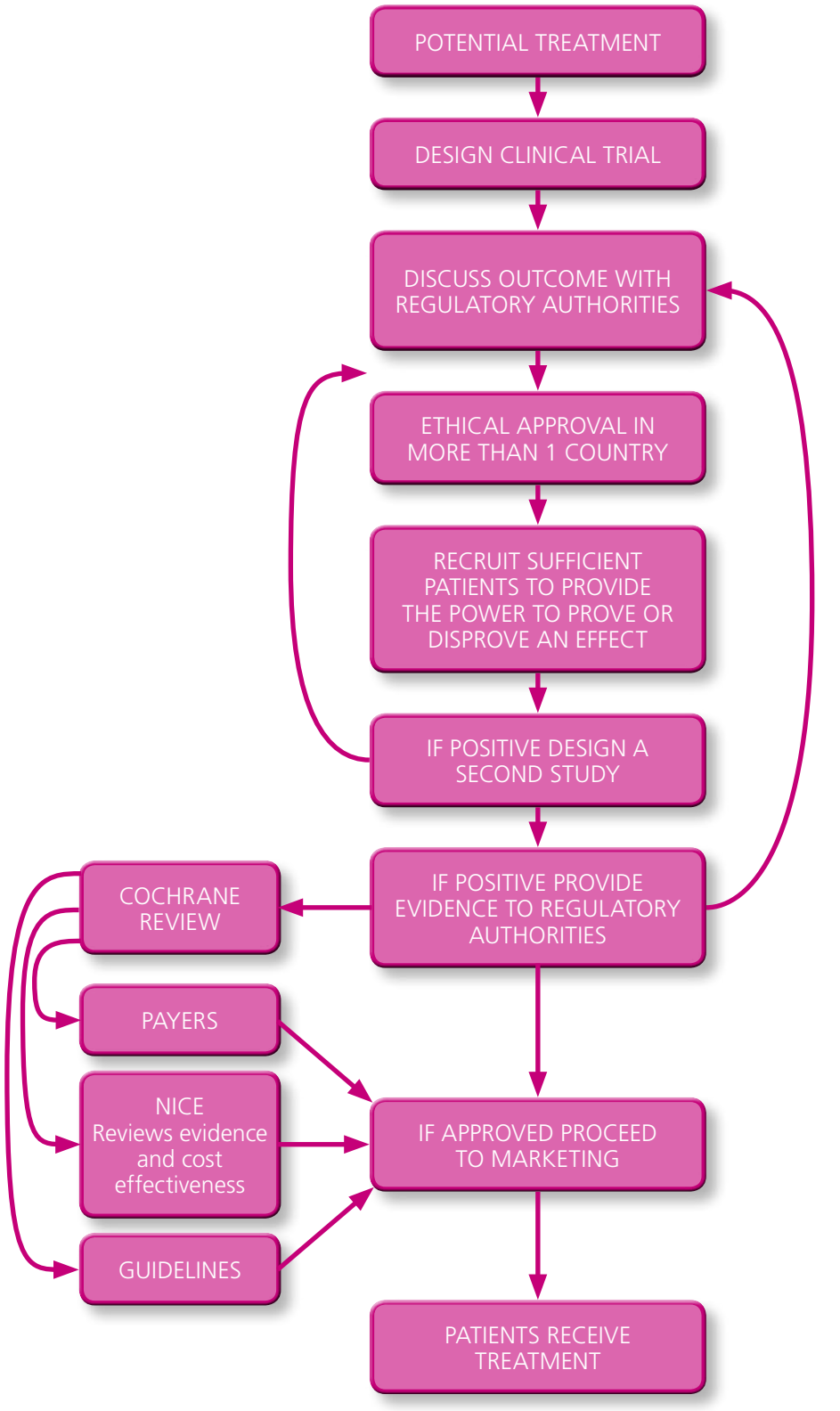
Interestingly out of this data analysis we showed that the average UK patient showed slower progression than those from other countries, when we combined our exclusive data

with that from other countries (ie. **a lot** of patients) we showed that lung function decline (FEV1) was slower in those receiving AAT than those not (an important observation but not a clinical trial).

So where are we? The overall belief of ADAPT and many worldwide experts is that AAT replacement works. However, selective review of the literature in the recent Cochrane review (usually believed to be an independent assessment) concluded that evidence of efficacy is still not robust. In the UK treatments (especially expensive ones) are not prescribed usually unless licensed (ie. approved by the regulatory authorities) endorsed by NICE and funding approved and released by the local NHS commissioners (who often use NICE as guidance). Named patient treatment can be received if endorsed by the patients doctors and approved by the commissioners. The alternative (as with lung transplantation) is that the government establishes and funds both assessment at national centres and the cost of therapy.

However, as always, wheels move slowly in the NHS and the continued accumulation of evidence is essential. Establishing the business case (and its cost effectiveness) is the future task. Meanwhile other treatment strategies are being explored as more than AAT is involved in this disease including the development and validation of simple markers that can predict whether the disease will remain stable or progress. Such tests will negate the need for several years of observation by just a single blood test. Some of the work is covered by the contribution of many of the team. Meanwhile I am pleased to see that the ADAPT patient group is now becoming well established and we will be working in partnership to achieve all these ends and an EU policy document is being prepared.

Flow diagram for drug discovery to treatment



Research

Update on Clinical Trials

Anita Pye
Clinical Trials Co-ordinator

November 2009, bags packed and off to Rome. Unfortunately not a nice sunny holiday but the Investigator Meeting for the Kamada Inhaled AAT study. We cannot complain though because there are much worse places to hold a meeting, although the Italian baggage handlers did decide to go on strike and some people ended up with no luggage for the duration of the trip, including the demonstration models of some of the study equipment!

It is quite an achievement to get the leading figures in the field of alpha-1 antitrypsin deficiency together and to be sitting in a room with them discussing a clinical trial is an interesting experience. The Project Manager talks us through all the aspects of the trial with an in depth look at what is required from the patient at each visit. There is training on the use of the electronic daily diary and the nebuliser that will be used to administer the study drug (this only turns up at the eleventh hour thanks to the Italian baggage handlers!). An Interactive Voice Response System is used to register each step of the subject's journey on the trial, including initial randomisation to receive either study drug or placebo. There is lively debate about the reasoning behind certain study procedures and after two days of productive discussion it is time to return to the UK, stopping for a quick look at the Coliseum on the way to the airport (well when in Rome and all that) and to start looking for potential participants.

The first patient was screened in January 2010 and to date we have screened 33 patients and randomised 26 patients to receive either study drug or placebo. As with all clinical trials not everyone who is screened fits the rigorous inclusion/ exclusion criteria for reasons which are beyond our control. Patients' safety always comes first and if there is any doubt at all that it might not be the best option then we would not include someone to simply make up the numbers. This particular study has seen a number of patients withdraw before completing the trial and this has been for a variety of reasons. As with any clinical trial you are always free to change your mind about participation and this would never impact upon your current or future medical care.

In April 2011 the first patient completed the trial at the site here in Birmingham, closely followed by a further four in the past couple of months. There have been no serious adverse events that have definitely been attributed to the drug and we are looking forward to finding out the results, although this will be a while yet as recruitment is still ongoing and the study consists of 12 months of treatment. We will not know who was taking drug or placebo until all the patients have finished the trial. The data is then checked and verified before the results are analysed. We will of course keep you informed.

The results of the EXACTLE (Prolastin®) and Roche (REPAIR) trials were eagerly awaited and finally released in 2008 and 2009 respectively. EXACTLE showed that a weekly dose of 60mg/kg was well tolerated and patients who received Prolastin® showed less progression on CT scanning compared to those who received placebo however this was only significant using one of 4 methods of analysis and has lead to doubts by some scientists/ doctors that a benefit was shown.

The REPAIR trial showed that a 5 mg daily dose was generally well tolerated relative to placebo but results also failed to show a significant effect in the entire patient population who received 1 year of treatment, although there could be a subgroup of patients who may benefit from receiving the drug. These results together with those from a 2 year study in patients with smoking induced emphysema , that is not caused by alpha-1-antitrypsin deficiency, will give us a clear idea whether the drug is likely to be beneficial for the treatment of emphysema.

Although there was no immediate breakthrough both showed encouraging signs for the future and the respective companies are working on the next steps in continuing and committing clinical trial strategies and potential treatments.

We do appreciate your continued help with clinical trials as it does require a great deal of commitment on your part but we can usually be flexible with clinic visits and do what we can to keep time in the unit to a minimum. As with all clinical trials there are always strict inclusion / exclusion criteria, which are determined by the sponsor company, so not everybody is suitable to take part. These vary for different trials so if you are not suitable for one trial it doesn't always mean you are not suitable for another. The criteria are set primarily to ensure the safety of those taking part so please do not worry if you are told you are not able to participate. Indeed, for the ongoing Kamada study we have had to turn a lot of willing volunteers down as they have not had enough exacerbations, and we realise that being told you are 'too well' to take part is a difficult concept.

I would like to take this opportunity to thank everyone who has taken part and look forward to welcoming more of you into the world of clinical trials in the future. If you are interested in ongoing and/or future trials please let us know and we will ensure that you are considered.

Research

Taking Part in a Research Study

We are carrying out a research project, as part of ADAPT, to try and investigate the changes in inflammation in patients with alpha-1 during exacerbations. We are looking for patients with the PiZZ phenotype who experience 2 or more exacerbations per year and wonder if you may be able to help.

What Would You Have To Do?

We would see you initially to go through a consent form (which could be done at your usual ADAPT appointment). Following this we would ask you to complete a daily symptom diary card. If your symptoms deteriorate for more than 2 days (which would indicate an exacerbation) we would ask you to contact us and you would be seen by a member of our team. We would collect blood and sputum samples, and perform a clinical examination. We would ask to see you again after 7, 14 and 56 days to collect further blood and sputum samples. Your usual treatment would continue as normal and we would provide advice, where appropriate, to your usual healthcare provider.

If you are interested in taking part, or would like some further information please contact:

Dr Anita Pye
(Clinical Trials Co-ordinator)
0121 371 3886

Mrs Diane Griffiths
(Research Nurse)
0121 371 3896

News

Alpha-1 UK Support Group Annual Meeting September 2011

The Alpha-1 UK annual support group meeting was held on the 10th September this year at the Burn Hall Hotel in York, many members made a weekend of the occasion and as usual it was an informative and fun filled weekend.

51 members and non members attended for the day where we enjoyed a delicious lunch and lively chatter.

Our thanks go to Professor Robert Stockley from ADAPT.

Dr Sandra Nestler-Parr from Talecris / Grifols and Yaron Cherny from Kamada who gave up their valuable time to give presentations and answered members questions. It was really interesting.

Later that afternoon we had our usual raffle and auction which is always good fun. Everyone was very generous and we were thrilled to raise £969.95 so a big thank you to all for their continued support.

At the AGM Previous Committee members were re-elected for another year and we were very pleased to announce two new Committee members had been elected.

On Sunday morning we bid our sad farewells until we meet again next year.

Alpha-1 Annual Support Group Meeting Plymouth September 2010

This year's annual support group meeting was held for the second year running at the Astor hotel in Plymouth. Although the main meeting is held on the Saturday many members make a weekend of it, we had approximately 45 members attend this year and as usual a great time was had by all. The weather couldn't have been better.

A presentation was made to John Doyle ...ill health has meant that some of John's workload as the group's Treasurer has been taken over by other committee members, but we wanted to show our appreciation to John for all his hard work over the years and for his 100% dedication to the support group. A bouquet of flowers was also presented to Mary, John's wife.

During the day we had a very informative presentation from Dr. Nicola Sinden and Nurse Diane Griffiths from ADAPT, bringing us up to date on the drug trials and research currently being undertaken by ADAPT. There was time for question and answers afterwards. Every one found it very interesting and we were very grateful for Nicola and Diane having given up their time to give the presentation, and for travelling so far to do it.

The hotel supplied a superb buffet lunch and afterwards, the afternoon was filled with fun, with quizzes, a huge raffle and the annual auction run by the group's very own Auctioneer Stephen (did I hear someone bid £20) Mayhew who, as always, does a such a great job extracting money from member's pockets and has the place in an uproar with his wonderful sense of humour. In total, the day raised approximately £900. The meeting broke up around teatime to allow members to get themselves ready for the evening festivities, which included a lovely three course meal followed by Karaoke which proved very popular.

Research

What is the significance of F alpha-1-antitrypsin?

Dr Nicola Sinden

Most patients who attend ADAPT have two Z alpha-1-antitrypsin genes (PiZZ) or a combination of an S and a Z gene (PiSZ). However, the ADAPT register also has a small number of people with the F gene. To date, we have 5 people with both F and Z genes (PiFZ) and 2 people with F and M genes (PiFM). Nobody with 2 F genes (PiFF) has ever been reported. Published information suggests that approximately 1 in 40 people carry the Z gene, whereas only 1 in 500 people carry the F gene. Since we have identified more carriers of the F gene than expected, it may be that the F gene is more common than figures suggest.

When blood tests are taken to measure alpha-1-antitrypsin (A1AT), normal levels may be found in individuals carrying the F gene. However, it is thought that F A1AT does not function as well as the normal M A1AT because individuals with an F and a Z gene may be at increased risk of emphysema. All 5 people with the F and Z genes on the ADAPT database have a level of A1AT that would be classed as normal. 3 of these individuals have abnormalities on the spirometry breathing test, 4 have abnormalities on the gas transfer test, 4 have two or more exacerbations per year and 4 have emphysema on CT scan.

Laboratory research has shown that F A1AT does not inactivate the damaging enzyme elastase as effectively as normal M A1AT, and is similar in function to Z A1AT. Individuals with an F and a Z gene (PiFZ) have similar blood levels of A1AT as those with an M and a Z gene (PiMZ). However, A1AT from PiFZ individuals takes 3 times longer to inactivate elastase than A1AT from PiMZ individuals.

I am carrying out further laboratory research into the function of F A1AT and its ability to inactivate the damaging enzymes elastase and proteinase 3. I would like to thank those PiFZ individuals who have given blood to make this research possible.

The importance of collecting sputum samples

Emphysema, chronic bronchitis and bronchiectasis are all lung conditions found in people with alpha-1-antitrypsin (A1AT) deficiency. These conditions are associated with inflammation in the lungs and increased numbers of white blood cells (neutrophils). An important part of our research at ADAPT involves measuring markers of inflammation in sputum samples which come directly from the lungs.

As described on page 12, proteinase 3 can be detected in sputum samples from people with A1AT deficiency. Our research has shown that people with higher levels of proteinase 3 in their sputum are more likely to have symptoms from their chest condition which impact on their daily activities. This particular test cannot be done on the blood samples that are taken, so without the sputum samples we would not have been able to carry out this work.

If you normally produce sputum, we would be grateful if you could bring a fresh sample along to your next appointment. Sputum pots can be obtained from your GP surgery, local hospital or we can send them out to you in the post.

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Healthy Controls

Much of our work trying to understand the processes that lead to or enable us to monitor health in AATD requires both patients and control subjects. This is important because many things about our health and how our body works will change with age. Thus we have to dissect things we find in patients from naturally occurring processes in order to be sure that they reflect disease.

For instance we now have a simple blood test that seems to indicate that the higher it is the more likely that emphysema will progress. However the test is also affected by age so we will need blood samples from healthy subjects of the same age to determine how specific the test is to predict future events.

Also there is some evidence to suggest that heart disease is more common in patients with COPD and the blood vessels become stiffer than normal. Again if this test is to predict who might develop heart problems we need to know what the normal ageing stiffness values are.

Control healthy subjects about the same age as our patients are therefore crucial for some of the studies we undertake. The best source of control subjects is the partner of the patient as they are about the same age and for every man we have a woman and vice versa. Thus, vital information can be gained from partners of COPD AATD patients by undergoing some simple tests and providing a blood sample.

If a relative would be happy to help with this please contact the ADAPT Team (0121 371-3885) and we can arrange to see them when you next attend for your annual assessment. We can provide an explanatory information sheet to help them understand what this involves.

Research

Bacterial Colonisation

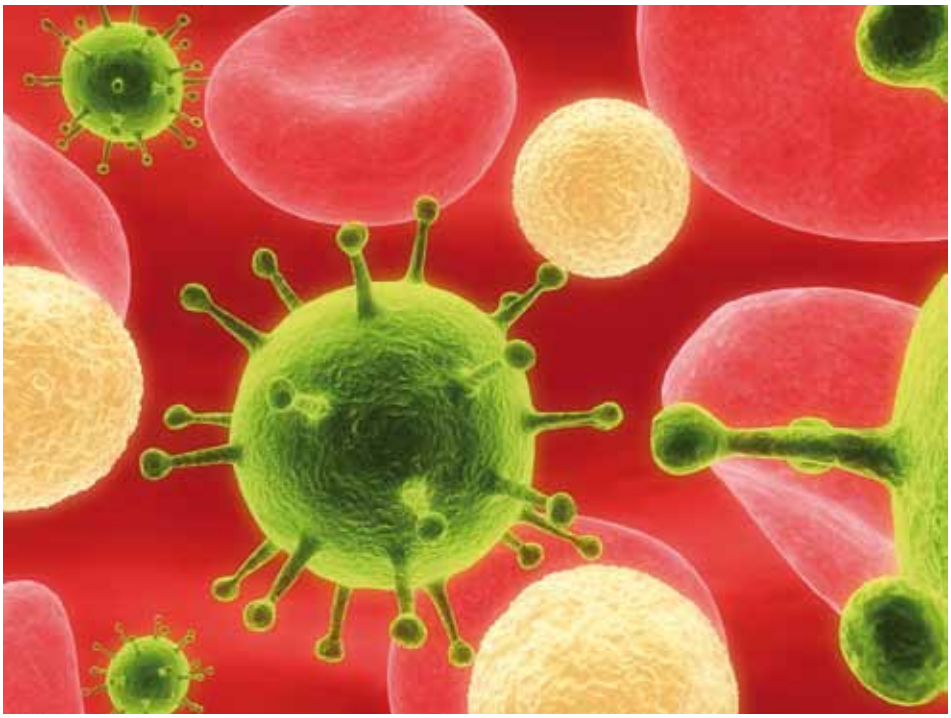
Dr Deborah Whitters

I am investigating the role of infection and bacterial colonisation in patients with chronic lung disease.

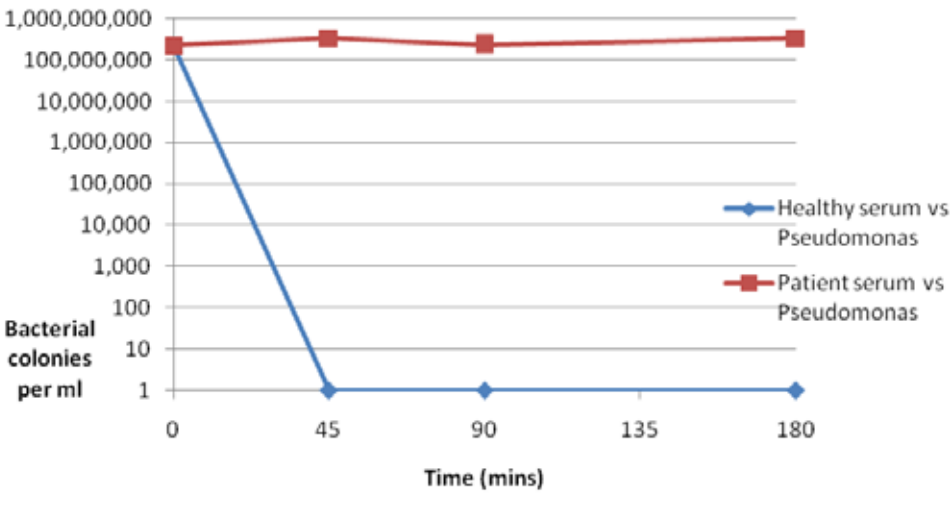
Bacterial colonisation occurs when patients repeatedly produce sputum samples which are positive for growth of a particular organism. We frequently see this in patients with bronchiectasis, including those with alpha-1-antitrypsin deficiency.

There are a number of factors which lead to bacterial colonisation. Specifically I am researching aspects of bacterial behaviour and interactions with the immune system, which enhance the ability of bacterial communities to colonise the lungs. Most of my research concerns a particular organism, *Pseudomonas aeruginosa*. This only tends to affect people with established chronic lung disease both with and without alpha-1-antitrypsin deficiency. However when it is isolated it can be very difficult to eradicate, is often resistant to a number of antibiotics and is associated with poorer quality of life and declining lung function.

In order to do this research it relies on blood and sputum samples from patients especially those with bronchiectasis. The liquid part of blood containing antibodies (serum), is then used in the laboratory to establish whether it can "kill" the *Pseudomonas aeruginosa* isolated from sputum samples. We also measure the ability of healthy control serum to "kill" the same bacterial strains. We measure this at regular time intervals by counting the number of bacteria present after it has been added to the serum. Thus far results have shown some differences as seen in the graph with some patient serum failing to kill *Pseudomonas*.



Future work is to look more closely at these bacterial communities to establish potential reasons for the differences we see between some patient serum and healthy serum and their ability to kill *Pseudomonas aeruginosa* in the laboratory. Once this is established we will be able to understand the reasons that bacteria grow in the lungs and develop new strategies to prevent this process. This should decrease the lung damage produced as the body tries ineffectively to remove the bacteria and the number of acute chest infections that occur.



Oxygen and flying

Dr Helen Ward

Air travel is common with the number of passengers increasing significantly over recent years. The number of long distance flights has increased as well as the duration of flights and the number of passengers that the planes are able to carry. Air travel in the vast majority of patients is safe but, in particular over longer distances, there are potential risks to the health of patients particularly those with existing health conditions including respiratory problems.

What happens to oxygen levels on planes?

Cabin pressurisation (the active pumping of compressed air into the cabin) is essential when flying at an altitude of over 3,000 metres above sea level to protect passengers and crew from the effects of low oxygen (hypoxia). The cabin air pressure is usually lower than at ground level (equivalent of flying between 2,000 and 2,500 metres) as it uses less fuel. At this altitude the oxygen is 25% lower than at ground level. Most passengers can tolerate this lower level of oxygen but if you have a respiratory problem you may need additional oxygen when flying.

How do I know whether I need additional oxygen?

It is important if you are planning to fly and have a respiratory problem, that you speak to your GP or hospital specialist before booking your flight. The British Lung Foundation advises that if you are able to walk 100metres on the level at a steady pace without shortness of breath or stopping then you are unlikely to require oxygen when flying. The British Thoracic Society published 'Managing Passengers with Respiratory Disease Planning Air Travel' guidelines in 2004 with an update due in 2011. These guidelines are for health care professionals and help identify which patients would benefit from oxygen when flying and to recommend those who should have a flight assessment. These guidelines take into account the patient's medical problems and oxygen level on air at sea level. If you already need oxygen then you will need oxygen for a flight without having to have a flight assessment and you are advised to contact your supplier.

What does a flight assessment involve?

Some hospitals offer a flight assessment to patients who may need oxygen on a flight. The oxygen levels are monitored, using an oxygen saturation finger probe, on air firstly then you are given 15% oxygen to breath for at least 15 minutes. This is the equivalent oxygen level that you would have at 2,500 metres (usual cabin pressure on a plane). If your oxygen levels fall below a certain level then it is recommended that you have oxygen when you fly.

What types of oxygen carriers can be taken on a plane?

There are several different methods for providing the oxygen you need on a plane:

1. Portable oxygen concentrators (POC). These work by sieving out the nitrogen from the air which passes through the concentrator and thereby supplying a higher concentration of oxygen. They are small and therefore portable. It is important if you are going to use a POC that it is an approved model (please contact the airline that you are planning to fly with for further advice).

2. Compressed oxygen in the form of cylinders.

3. Liquid oxygen is not permitted on flights as it is easily combustible.

I need oxygen. What do I do next?

If you are advised that you need oxygen during a flight then it is recommended that you contact your airline directly as early as possible. Airlines have different

Different methods for providing the oxygen you need on a plane

requirements for patients needing oxygen.

When you speak to the airline it is important to ask these questions:

- Do they have a special department to speak to about the oxygen?
- Do they accept passengers who need oxygen?
- How much notice do they require before travelling?
- What documentation is needed?
- Do they charge for oxygen? (Be aware that some airline companies do not let you bring your own oxygen on to the plane and also charge you for providing oxygen)
- Are there specific seat requirements?
- When do the oxygen arrangements need to be confirmed?

The oxygen only needs to be turned on when at cruising altitude and switched off at start of the descent.

What services are available?

1. Portable oxygen concentrators. These can be hired from specific companies including Intermedical or pure O2, can be bought and also the patient group Alpha-1-UK has an oxygen concentrator that can be hired for short haul flights within the European Union.
2. Oxygen cylinders. These can be rented from oxygen suppliers e.g. Air Products.

What else do I need to remember?

- Ensure you have additional travel insurance (to cover cost of any necessary return by air ambulance).
- Ensure your inhalers are in your carry-on bag.
- Drink plenty of water during flight.
- Leg exercises during the flight.
- If stopping over you are responsible for your own oxygen.
- MOST IMPORTANTLY enjoy your holiday!

Where can I find more information about oxygen and flying?

The British Lung Foundation (BLF) has

2 booklets available to order or print from their website free of charge:

- Health Information Booklet 'Going on holiday with a lung condition'
- Information Sheet 'Air Travel'.

Testing at Birth

Professor R. A. Stockley

The simplest and most logical way to identify all subjects with alpha-1-antitrypsin deficiency is to test them at birth as part of the heel prick blood test for rare metabolic diseases. However as with all good ideas the number of hoops we need to jump through are many.

The first step was to write a case for the testing. This was followed by an extensive and complex form including data on the economics of the test, laboratories that could do it and the cost benefit of finding people before they start to smoke.

The simplest and most logical way to identify all subjects with alpha-1-antitrypsin deficiency is to test them at birth as part of the heel prick blood test for rare metabolic diseases.

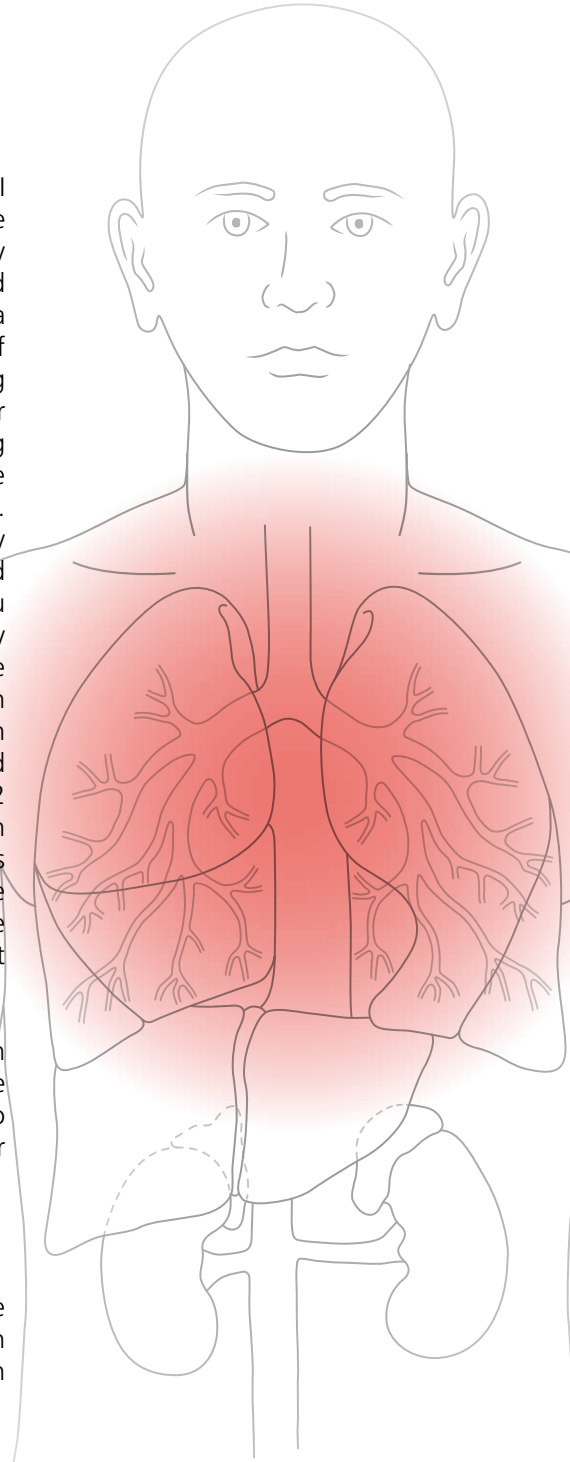
The next step was to answer queries and modify the form and then we had to arrange a meeting and presentation to the genetic disease committee in London. At the end of this meeting they raised many questions, most of which we had answered on the form and told us they would send a report for us to rewrite and resubmit the original form and then meet the committee again.

Well we still await the report, the government has changed and all things medical have gone on hold. Still! We need to push on if anything is to be done about this (another email!)

Research

Evaluation and Control of Lung Inflammation assessed with PET scanning in Emphysema and Alpha-1-Antitrypsin Deficiency (ECLIPSE AATD)

Paul Avison



How I came to do. it

From the time I saw a report on BBC Midlands Today of Prof Stockley's ROCHE (Repair) trial in 2007, I wanted to get involved and find out more about the ADAPT project. As an emphysema sufferer with alpha 1 antitrypsin deficiency I hoped that I could volunteer for one of the trials being undertaken. Taking part in a trial seemed to me the best way to learn about my condition, understand the latest thinking on treatments and possibly even be a beneficiary of any breakthrough!

Following a number of e-mail and letter exchanges with doctors Anita Pye and Deepak Subramanian, in Jan 2009 I was asked to visit the ADAPT team at the QE in Birmingham to take part in the ECLIPSE AATD trial.

Brief description of the trial

This trial sponsored by Talecris aimed to study the effective take up of 'Prolastin' by the lungs, after 12 weeks of weekly infusions of the drug, as measured by a PET scan at the beginning and end of the trial.

Without naturally produced antitrypsin protecting the lungs, they become easily inflamed so measuring the outcome by way of the PET scan was crucial to seeing if this infusion approach worked. To ensure the accuracy of the trial there was, in addition to AATD sufferers, an emphysema group without AATD and a control group with no lung problems.

Interview and assessment

The January visit enabled me to meet the ADAPT project team and provide Deepak (with my wife's help!) details of my experience with my lung condition. I had lung function, x-rays, ECG and blood tests in a relaxed and very friendly atmosphere at Nuffield House, and at the end of these I was declared 'fit' to take part.

Weekly sessions

Towards the end of March last year I was one of the first of thirty people to commence in the trial, and have my initial PET scan and first infusion. I had had a CT scan once before but never a PET scan so the procedure was a bit of a novelty. The process involved receiving a radioactive marker through a catheter in my left arm, and blood samples being taken from my right arm at 8 minute intervals during the scanning process. An initial CT scan followed immediately by the PET scan took about an hour and would have been very boring (if you can't sleep through it!), but thankfully the staff of the scanning centre gave me a music CD from their selection, to listen to. Later that day I had my first infusion of Prolastin and blood sampling, and this was usually administered over the 12 weeks by Diane and Ross. Each session was supposed to take about 30 minutes but generally took longer because we ended up gossiping with most of the team who happened to be around at the time.

In June, at the end of the infusion process, I had my second PET scan. The results from both scans were then to be evaluated along with all the other differing participant groups.

Assessment: the trial and beyond

The trial has now finished and all the results are being evaluated in conjunction with other alpha1 / COPD trial centres in the UK, Europe and US.

I understand from Deepak that there have been some surprising findings from the PET scanning, and I assume probably raising more questions and investigations, and who knows what these might lead to?

I (and my wife Mary) feel very privileged to have been part of this trial and I will gladly take part in suitable trials in the future. It is very comforting to know that I am now one of a large group of fellow alpha 1 deficient people, who are under the watchful eye of the ADAPT team, and benefit from an annual health-check.

Patient Story

Trials and Tribulations

Alan Booty

In September 2007 I had the opportunity to be a patient delegate in Rome at a conference of research and support groups involved in Alpha1 antitrypsin deficiency. Representation was from 21 countries, proving that to be really breathless you had to learn to gasp in at least three languages.

As a delegate I quickly realised that I was amongst specialists who used words I'd never heard of so any thoughts I had for simplicity rapidly hit the rocks. However, they all stated that their work defining treatment and ultimately prevention was in the end entirely reliant on active patient involvement. Simply 'you can't prove it unless you've tried and tested it'.

Since then I became involved in the Roche evaluation but had to be withdrawn mid programme because of a potential problem and although that concern proved unfounded it did demonstrate the other important issue of patient safety.

January 2010 didn't started off too well when I was admitted to hospital with a good old dose of pneumonia with added pulmonary embolisms for luck. Having to be in hospital came as a bit of a shock and being in a ward with five other chesty people I quickly learned that you had to resist the offer of one of the two beds by the windows. Whether it was the howling draught or the mortuary assistants need to keep you in proximity to the exit door, the 'going out feet first' rate seemed to be a high charge just for a view so I valiantly waved off their advances. As with Alpha 1, infection inevitably brings further loss of lung function and nearly four weeks later I was discharged now having to get used to oxygen as part of the daily diet.

It was shortly after that I was contacted by ADAPT to see if I was interested in becoming involved in the Kamada trial. I was still feeling pretty sorry for myself and the thought came to me that there's life in the old dog yet.

For the technophiles, the Kamada trial is for you and there's basically two bits to it - the drug or its placebo, which you inhale twice a day as near as possible 12 hours apart using an ultrasonic nebuliser – and an electronic diary, which you fill in once a day. Along with the nebuliser you get a steam steriliser (baby bottle type thing) to clean the nebuliser once a day. It's also good for steaming vegetables – spinach is brilliant.

The ultrasonic nebuliser is very easy to use, it's small, robust and silent and compared with the old compressor driven things, a dream. It uses standard AA batteries but to be honest they don't last long and unless I was away somewhere I plugged it into the mains with the supplied transformer. An inhalation does take a while - about 15 minutes so it's about a twenty minute process twice a day plus a sterilise which is a twenty minute job which it can do on its own but I coincided the inhalations with reading the newspaper or doing a crossword – the newspaper also soaks up the dribble which I find an unavoidable by-product of breathing though a mouthpiece.

The electronic diary is an adapted palm pilot PDA and an entry has to be made in the diary before midday each day and has an alarm to remind you. Connection to download the entries can be either by land line or wireless and you can store a good number of entries before down loading - my average was one download every six days or so but it can take many more.

The diary has a set of questions where you have tick boxes to complete and asks you questions about how you feel, whether you have consulted anyone or visited a hospital, whether you have altered your drug regime and so on. All the questions are subjective and very much relate to your pulmonary condition not whether your leg has fallen off. What bemused me was the 'did you sleep well' question, which specifically relates to whether you were woken up by your breathing difficulties.

Picture the scene – out of a sense of genuine friendship you have offered to look after your neighbour's two children while they go off for the weekend to learn needlepoint. The youngest decides to escape and the older one who you didn't know had pyromaniac tendencies has set ablaze your priceless collection of dried rhubarb cuttings It's three o'clock in the morning, half your house has burned down – a child protection officer is restraining you after you threatened the older child with the smouldering remains of your once beloved cricket bat.

For the purposes of the diary - you 'slept well'

For my part my first visit was in March 2010 for screening and then a re-screening in May. I started using the electronic diary in April 2010 and finished in June 2011. I had my first dose of study medication in June 2010 with my last at the end of May 2011 with a follow up review in June 2011. During the study period I had six visits to ADAPT with progressively increasing time spans between visits as the study progressed. Apart from the stuff I picked up at the visits, monthly deliveries of drug were by courier. On the last visit I had three insulated drug boxes to return, one steriliser and one nebuliser kit – all this plonked on a sack truck to the intrigue of the security bloke at the door to the hospital.

So what was in it for me?

Back in January 2010 I had a good old brush with mortality and frankly the Kamada programme gave me twelve months to think my health forward. Yes, sometimes it was a bit of a fiddle and it does demand getting close to three quarters of an hour a day but personally I go back to 2007 to the conference and the things I learned there

There are all sorts of things that individuals suffering from the impact of AATD can do to sustain and improve quality of life

- Rehabilitation and exercise to maintain physical strength and endurance and to reduce breathlessness (progressive reduction in activity is the hallmark of COPD)
- Nutrition (maximise healthy energy intake)
- Management of tension and anxiety (the less anxious the less breathlessness)
- Augmentation therapy (oxygen / perhaps surgery)
- Avoiding infection (infection creates damage)
- Don't give up
- Do a drug trial and give someone else a better life.

Research

Proteomics in Alpha-1-Antitrypsin Deficiency

Dr. Helen Stone

What is Proteomics?

Proteomics is the study of the proteins present in an organism at a given time. It typically uses a mass spectrometer to do this, which is a way of separating proteins based on their size. Proteomics offers a way of looking at as many proteins as possible in a sample, which is and can be used on lots of different samples including blood, urine, tissue and sputum.

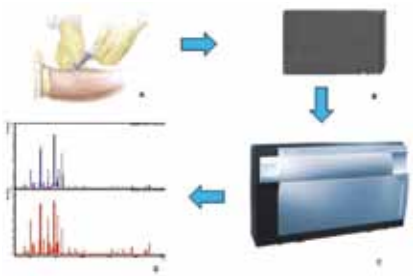
Why Could Proteomics be Useful in Alpha-1-Antitrypsin Deficiency?

In patients with alpha-1 antitrypsin deficiency, the blood levels of alpha-1 are low. As a result, the lungs are more vulnerable to the effects of an enzyme known as neutrophil elastase, which is released from white blood cells. This means that there is damage occurring in the lungs breaking down the lung tissue and causing emphysema.

My Work so Far

As a part of ADAPT and the other clinical trials we run, we routinely collect and store blood samples. Blood is one of the most useful samples to analyse using proteomics, as every tissue and organ in the body has a blood supply, so changes within any of them are theoretically detectable in the blood. I am looking at the proteins in samples from 2 studies- the EXACTLE trial, where patients received either Prolastin (intravenous alpha-1 replacement therapy) or placebo over a period of 2 years, or the PET study, which included patients with alpha-1 before and after 3 months of treatment, patients with usual COPD and healthy controls. I am specifically looking at proteins which change which could act as a marker of a response to treatment with Prolastin. To do this, I am working with the Proteomics Department at the University of Birmingham, who have recently installed state of the art equipment. A diagram of how this works is shown below.

In theory this sounds straightforward although the reality is quite different as I have discovered. The more state of the art equipment is the more temperamental it seems to be. However despite these setbacks, this is providing valuable information on these blood proteins and how they change in alpha 1 antitrypsin deficiency.

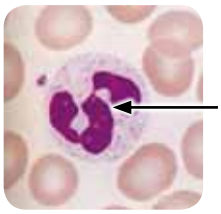


The diagram above shows a typical workflow of my experiments. Blood is taken (A) and then prepared for analysis by removing the proteins. A small amount is then placed onto a spot on the steel plate, (B) which is then placed inside the mass spectrometer (C). A laser is fired at the sample, causing it to be accelerated to a detector. A spectrum is then given, (D) which shows a number of peaks, which represent the number of different proteins found within the sample along with their size. In this picture a pair of samples is shown – before (blue) and after (red) treatment samples from patients who took part in the ECLIPSE A1ATD study. I am currently analysing this data to see if there are any differences after treatment.

Proteinase 3

Dr Nicola Sinden

Alpha-1-antitrypsin (A1AT) deficiency is associated with emphysema. With this condition, inflammation in the lungs leads to increased numbers of white blood cells (neutrophils). Neutrophils release substances (proteinases) that help to fight infection in the lungs, but if the activity of these proteinases is not controlled they can damage lung tissue. Levels of proteinases are high during chest infections, and that is why it is important to treat bacterial infections promptly with antibiotics. A1AT inactivates proteinases, and therefore if the levels of A1AT are low there is the potential for proteinases to do more damage.



Previous research has studied one of the proteinases (elastase) in lung diseases. However, another proteinase (proteinase 3) has not been well studied. Proteinase 3 may be important in emphysema, particularly when associated with A1AT deficiency. Firstly, neutrophils contain more proteinase 3 than elastase. Secondly, A1AT is more likely to inactivate elastase than proteinase 3, so if levels of A1AT are low this may allow proteinase 3 to cause greater lung damage.

My work aims to study proteinase 3 in greater detail using blood and sputum samples taken at ADAPT appointments. I will study neutrophils from A1AT deficient individuals and healthy people to measure proteinase 3 release. I will also measure the activity of proteinase 3 in blood and sputum samples and compare this to elastase. By increasing understanding of the important roles of different proteinases in emphysema, this may assist in the development of new specific treatments.

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alpha-1

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Research

Tumour necrosis factor-alpha gene abnormalities in Alpha-1-Antitrypsin Deficiency – how relevant are they?

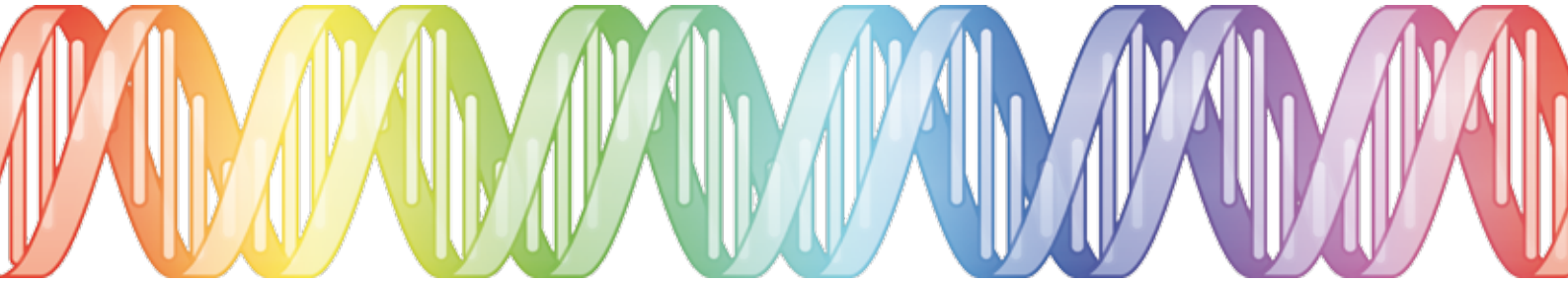
Dr Jennie Gane

We know that alpha-1-antitrypsin deficiency affects people in different ways. Some have liver disease, most have emphysema and others have bronchitis, asthma or bronchiectasis. This all suggests that other genes also play a role in determining the type of lung disease that develops TNF-alpha is a cytokine (a protein chemical messenger) produced by white blood cells as part of the body's immune response to either infection or irritants such as cigarette smoke. Our research group, among others, have shown that along with other chemical messengers, TNF-alpha plays a role in COPD and COPD due to Alpha-1 Antitrypsin Deficiency. TNF-alpha is released into the lung tissue and airways and the blood stream and drives inflammation and weightloss but also helps to attract and encourage white blood cells such as the neutrophil, which cause lung damage.

It is possible to inherit a slightly different form of the gene (a gene polymorphism) which codes for the TNF-alpha protein, compared to that which most people have. Previous clinical fellows here at the ADAPT project (Dr Alice Wood and Dr Liz Sapey) identified that a small proportion of people with Alpha-1 Antitrypsin Deficiency also have this different form of the TNF-alpha gene. Sputum samples from eleven of these patients contained very high concentrations of the TNF-alpha protein and other chemical messengers, including those produced by neutrophils, compared to sputum from other Alpha-1 Antitrypsin deficient patients. The patients were highly likely to have cough and sputum production (80% of patients compared to 30% without the gene polymorphism). In addition the patients were thinner (having lost weight) and their lung disease progressed more rapidly. This suggests that the immune response going on in the lungs of Alpha-1 Antitrypsin patients with this genetic polymorphism might be different in some ways and importantly could respond to drugs that block the TNF-alpha protein.

TNF-alpha blocking drugs have been shown to work well in other conditions where the protein plays a role in driving the immune response, for example in rheumatoid arthritis. However, a trial of these drugs in a general COPD population did not have any benefit but this was not surprising as most COPD patients have normal TNF-alpha. It is likely therefore that only those with the abnormal TNFa gene and hence high levels of TNFa will respond.

My research project will involve further study of the immune function of Alpha-1 Antitrypsin patients who also carry this uncommon form of the TNF-alpha gene. In particular I will be looking at the function of their monocytes, another important white blood cell in COPD. I will be using the monocytes to see how much TNF-alpha and other mediators they produce in response to different stimuli, how well the cells digest bacteria (phagocytosis) and how efficiently and quickly they move (chemokinesis). I will also study the effects of incubating the cells with a TNF-alpha blocking drug to see if this alters their function. If we continue to find differences in cell function between these patients and those without the TNF-alpha polymorphism we plan to carry out a small clinical trial in the affected patients using a TNF-alpha blocking drug. It may be that the previous trial using this drug was ineffective because the "right" patients need to be targeted to receive it.



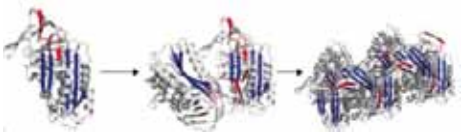
Research

A model for alpha-1-antitrypsin deficiency

Dr Gillian McNab, Research Fellow
Respiratory Research Laboratories,
Clinical and Experimental Medicine,
University of Birmingham

There is currently no cure for alpha1 antitrypsin deficiency (α_1ATD). At present the only available option for treatment include replacement of the blood α_1AT intravenously every week. However substitution therapy is limited by several factors: therapy requires weekly intravenous infusions and patients often need to visit a health care institution for treatment; only a small proportion of intravenously administered α_1AT reaches the lung tissue and its role in preventing progression of lung disease remains unproven. Suitably powered conventional clinical trials are also lacking which limits the availability of intravenous therapy in many countries. Clinical trials can be difficult and time consuming to carry out and often have criteria which mean that not all patients with the disease can be studied. They also require a lot of information to be gathered about individuals which may not be routinely available.

Nevertheless, augmentation therapy (even if effective) would not protect the liver from accumulated protein. Other alternatives still being tested in the lab include gene therapy, where the normal α_1AT gene is delivered into the lungs; the development of drugs to prevent the protein blocking up the liver and the introduction of small peptides that stop the α_1AT forming chains (polymers). These approaches may offer some lung-protective benefits by increasing the concentration of the α_1AT in the blood and may prevent the liver disease by releasing α_1AT although the α_1AT released may not be active.

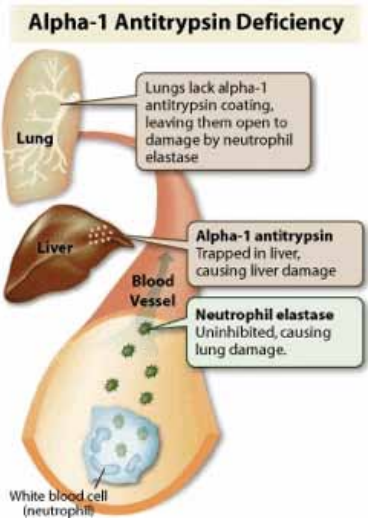


Single α_1AT molecule

α_1AT molecules forming chains (polymers)

Basic understanding of the mechanisms involved and treatment of α_1ATD have been hampered by the lack of a specific animal model. The α_1ATD mouse models currently available have several drawbacks and none of them mimic the human genetic defect adequately for early studies of disease progression and development of treatment strategies. My current research involves the development of a unique animal model of α_1ATD by replicating the human Z deficiency in mouse α_1AT genes, which in turn will create the mouse equivalent of human disease. I have made both the normal and α_1ATD mouse proteins and found that they behave in the same way as human α_1AT. I have also tested a treatment which reduces polymer formation of α_1ATD in man. I found that this treatment reduces the formation of polymers of the mouse "Z" protein. It also increased the levels of mouse "Z" α_1AT secreted and specifically reduces the accumulation of the mouse "Z" protein in cells.

The mouse model will have the following characteristics:-

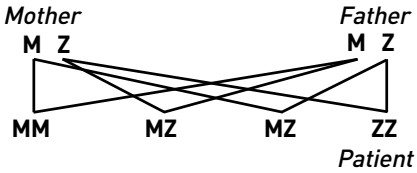


The development of this unique and novel mouse α_1ATD model is urgently needed in the field. The final outcome of the project will be a significant advance in both our understanding of the disease process, diagnostic procedures and drug development, including routes of administration. The major benefits of this research will be for patients with a1ATD, as successful treatments and therapies which work in the mouse model have high potential for being translated into the clinic, moving the progress in developing treatments in patients forward and demonstrating effective therapies faster.

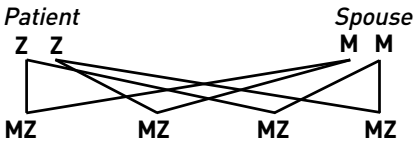
I have also been developing a strategy that reprograms white blood cells (monocytes) into liver-like cells. If successful, these liver-like cells can also be used in my gene correction studies, which normalises the α_1ATD gene and α_1AT levels, and for testing the potential efficacy of novel treatments.

Alpha-1-Antitrypsin Inheritance

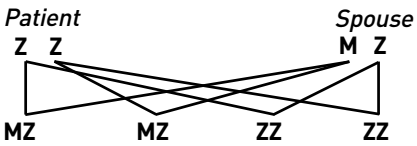
Alpha-1 Antitrypsin Inheritance



The likely family history of a patient identified as Pi Z, giving a 1/4 incidence of the siblings being Pi M, a 1/4 incidence of Pi Z and a 2/4 incidence of Pi MZ.

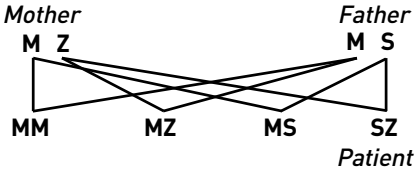


Implications for the patient. With a 90-95% chance that the spouse will be normal (Pi M), indicating that all children should be Pi MZ.

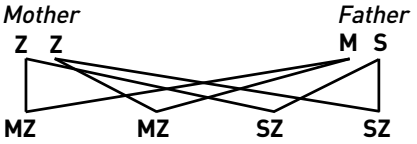


Implications if patient marries a heterozygote (approximately 3-5% chance). Again, one allele will be passed to the children from each parent with a 1/2 chance that offspring will be Pi MZ and a 1/2 chance that offspring will be Pi Z.

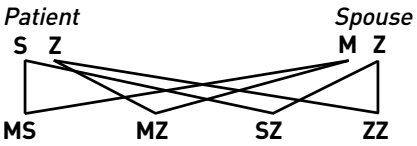
Alpha-1 Antitrypsin Inheritance (SZ Phenotype)



The most common family history of a patient identified as Pi SZ. Both parents are usually partially deficient, one being MZ the other being MS, which results in a 1/4 incidence of the Pi SZ phenotype together with a 1/2 incidence of partial deficiency.



Occasionally patients who are Pi Z can have children with a partner who is partially deficient for the MS phenotype. This results in a 1/2 chance of children having the SZ phenotype and the remaining children being less affected with the partial MZ deficiency.



Most patients with the SZ phenotype will have a normal partner with the M phenotype, which means that all other children will be either MS or MZ. However, there is about a 1/30 chance of the partner being partially deficient of the MZ type and this will mean that none of the children will be entirely normal. There is a 1/4 chance of each child having severe deficiency of the Z type, a 1/4 chance of a further child with the SZ phenotype and finally a 1/2 chance of partial deficiency of the MS or MZ type.

Useful Information and Contacts

www.alpha1.org.uk
www.aatregistry.org
www.lunguk.org
www.brit-thoracic.org.uk
www.expertpatients.co.uk
www.alphaone.org

Getting Oxygen in the UK and abroad

Your UK oxygen supplier will be able to help you to get oxygen in the UK and abroad. Speak to them well in advance for details, including how to get help should you need it while on holiday. Some patients require an oxygen assessment to determine if oxygen is needed on aeroplanes. You should ask your doctor about this.

www.airproducts.co.uk
www.bocmedical.co.uk
www.flying-with-disability.org/oxygen.html

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