

What then can we learn from this story and how can we move the field of new drug development in refractory asthma forward? One obvious but important and often overlooked priority is to study the correct patient population and choose the right outcome measure. Thus if one is investigating an anti-eosinophil treatment, it makes sense to begin investigation in a population with severe eosinophilic airway inflammation and choose an inflammation related outcome measure such as exacerbation frequency. In contrast, if the major effects of the investigational agent are on airway smooth muscle function (as seems to be the case with anti-TNF α treatment), then a better population would be those with severe and corticosteroid resistant airway dysfunction, and better outcome measures would be symptoms, variable airflow obstruction and airway hyperresponsiveness. Another important priority is to identify biomarkers of treatment response. In our initial study the beneficial effects of etanercept were closely related to peripheral blood mononuclear cell membrane TNF α expression.²¹ Whether this biomarker can be used to identify a population where anti-TNF α treatment can be used effectively and safely should be investigated.

At a later stage in development, or if the main effects of the investigational agent are unclear, then it is important to evaluate a sufficiently large and well characterised population for relationships between baseline demographics, potential biomarkers and treatments response to be identified. Considerable thought should

be put into recruitment criteria with the emphasis more on identifying and including the at need population and less on recruiting a pure population based on arbitrary clinical and physiological criteria. If we can do this, we will learn more about the pathophysiology and heterogeneity of refractory asthma and we may have more to offer a group of patients who currently have considerable unmet needs.

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Pleurodesis for malignant pleural effusion: talc, toxicity and where next?

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Malignant pleural effusion accounts for 22% of all pleural effusions, and affects about 300 000 patients annually (UK and

USA). Approximately 50% of patients with breast cancer, 25% of those with lung cancer and >90% with pleural mesothelioma develop a symptomatic malignant pleural effusion. Thoracentesis provides effective short term symptomatic relief but most large malignant pleural effusions recur,¹ and pleurodesis is then the standard treatment. A wide range of compounds have been used as

pleurodesing agents, but talc is preferred by the majority of respiratory physicians worldwide.²

The Medicines and Healthcare Products Regulatory Authority (MHRA) has recently completed an urgent review of the safety of talc as a pleurodesis agent for malignant effusion, reclassifying it as a medicinal product rather than medical device.³ This review requires that from January 2008, manufacturers must submit regulatory data if they wish their talc preparation to be used for pleurodesis. This is a milestone on the path towards improved care for malignant effusion as it heralds the first time an agent for intrapleural administration will be regulated under the systems used for biologically active drugs.

Talc is a magnesium silicate hydroxide (Mg₃(Si₂O₅)₂(OH)₂) and is mined, milled and sterilised prior to clinical use, although

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these processes still sometimes leave behind mineral or organic contaminants. The MHRA review was a response to evidence that some of the preparations produced by these processes, and considered safe for pleurodesis in the UK and USA for over 50 years, are in fact anything but. Pleurodesis preparations not sorted to remove most of the smallest talc particles (widely used in the UK and USA) are associated with clinically important hypoxaemia in humans,⁴ induce systemic and pulmonary inflammation after being absorbed from the pleural space⁵⁻⁷ and were associated with death from respiratory failure in over 2% of patients when used for pleurodesis in a large US clinical trial.⁸ Preparations with the smallest talc particles removed (graded talc) are associated with a reduction in this risk. In a European cohort study of 558 patients treated with graded talc, no frank episodes of acute respiratory distress syndrome occurred. Assuming that it is small talc particles which are truly causal of acute respiratory distress syndrome (and not, for example, contaminants) changing to graded talc may avert up to 250 unnecessary deaths each year—a significant improvement in care.

The lesson that intrapleural therapies can cause unexpected systemic toxicity and needs to be thoroughly assessed to ensure safety is not limited to talc. Intrapleural iodopovidone, for example, can cause visual loss⁹ as well as severe chest pain and hypotension.¹⁰

WHERE NOW FOR TALC?

Despite the substantial safety improvement that will follow the use of graded talc, some residual questions about safety still remain. Even in the European cohort study¹¹—seen as the strongest evidence of graded talc safety—7/558 (~1.5%) patients developed radiographic pulmonary infiltrate after talc administration. There was also a general increase in post-procedure oxygen requirements, which is consistent with the hypoxaemia seen in a subset of subjects after graded talc administration in human physiological studies.⁴ This hypoxaemia is despite the procedure being one in which substantial pleural effusions are drained, and improvement in respiratory function would be expected. These pointers hint at some residual pulmonary toxicity despite removal of most small size talc particles, and imply that vigilance for talc associated lung inflammation should be maintained in the future.

The “post-marketing” adverse event monitoring for talc will be regulated by the usual drug monitoring systems. This will encourage the highest standards of

quality control as licensing will require the achievement of prespecified product standards. For talc, this seems likely to include levels of impurities and particle size. Achieving these standards will probably raise manufacturing expenditure and alter the balance of market forces, increasing the cost of “medical grade talc” in clinical use. This is the inevitable price of higher quality patient care.

WHERE TO FROM HERE?

The focus these changes will bring to pleurodesis may also spur the search for new and better pleurodesis agents. The development of pleural symphysis is a multifactorial pathway with initial inflammation and subsequent fibrosis which obliterates the pleural space. Strategies to target specific cellular mediators of the pleural inflammatory cascade are already beginning to translate into clinical trials, and efforts focusing on the development of pleural fibrosis without inflammation are ongoing.

In animal studies, intrapleural preparations of the potent profibrotic cytokine transforming growth factor β produce an effective pleurodesis.¹²⁻¹⁵ Human trials of this agent are awaited. Less selectively, several bacterial proinflammatory moieties are being explored in an attempt to therapeutically mimic the potent pleural fibrosis induced by bacterial infection. OK-432^{16 17} (derived from *Streptococcus pyogenes*) has been used in Asia for several decades, although experience of its use elsewhere is limited. *Staphylococcus aureus* superantigen,¹⁸ and motifs derived from other gram positive bacterial cell walls, have both entered early clinical trials, although definitive studies to define their efficacy and toxicity are awaited.

IS AN ENTIRELY DIFFERENT THERAPEUTIC APPROACH WARRANTED?

If an ideal pleurodesis agent that is capable of effectively controlling fluid and free from significant adverse effects does not exist, it seems reasonable to consider entirely different management strategies for malignant effusion, and to reconsider the definition of “successful” treatment. Clinical trials have tended to focus on pleural fluid recurrence or the extent of pleural symphysis as surrogate markers of success. However, breathlessness relief, and maintaining patients’ quality of life, is actually the aim of care for these patients, and this should be the clinical trial outcome of choice.

Subcutaneously tunnelled, indwelling pleural catheters are an accepted component

of care for patients with symptomatic effusions who have failed pleurodesis, or where the lung is incapable of re-expansion.¹⁹ The firstline use of such a type of catheter could permit entirely outpatient care and patient controlled fluid drainage, albeit at the cost of the catheter and drainage equipment, and potential adverse events associated with the presence of the catheter. Initial early and effective fluid drainage may also reduce the likelihood of the development of multi-septated symptomatic and difficult to evacuate effusions, which can be the result of ineffective chemical pleurodesis. Spontaneous pleurodesis rates of up to 70%²⁰ following use of these catheters have been reported in non-randomised data, and patients’ quality of life/sense of empowerment may also improve as a result of this approach.²¹⁻²³ A British Lung Foundation funded clinical trial is currently addressing some of these issues and comparing the efficacy and safety of patient controlled fluid drainage by indwelling pleural catheter with standard care.

Other non-pleurodesis based options include use of a pleuroperitoneal shunt, although the need for surgical insertion and potential shunt occlusion are disadvantages to this strategy. Surgical pleurodesis (ie, parietal pleurectomy and pleural abrasion) is effective although limited to patients of exceptionally good performance status and prognosis.

CONCLUSION

Reclassification of talc for pleurodesis as a drug is a positive step. It is likely to directly improve the safety of talc pleurodesis by influencing particle size and impurity levels, and bringing it in line with all other human medicinal products. The talc debate may also spur the development of new, better pleurodesis agents, and perhaps the complete reshaping of some aspects of care for malignant pleural effusion.

Competing interests: RJOD and HED hold/have an interest in the patent rights for the use of lipoteichoic acid- t for pleurodesis, and Rocket Medical have donated indwelling catheters to a BLF funded clinical trial assessing this therapy that is led from the Oxford Pleural Unit.

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Are we understanding the respiratory effects of traffic related airborne particles?

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There is convincing scientific evidence showing that ambient particulate matter (PM) is related to both short and long term health effects. Increased mortality and hospitalisation for cardiopulmonary causes have been noted in several studies evaluating the effects of PM₁₀ or PM_{2.5} (PM <10 or 2.5 µm in diameter).¹ However, urban air pollution consists of a complex mixture of gases and particulate agents that vary over time and through space, depending on its sources, distance and meteorological conditions.² Much of the scientific interest has been devoted to the toxicology of the ultrafine fraction of airborne particles (<0.1 µm).³ These particles are usually emitted from combustion sources (eg, gasoline or diesel powered engines) or are formed from chemical conversion of gases in the atmosphere. They are relatively short lived and combine into larger particles between 0.1 and about 1 µm in diameter (accumulation mode). These particles tend to penetrate deeper in the alveolar part of

the lung and have a larger surface area than larger sized particles, eliciting greater potential interaction with human tissues and a stronger inflammatory reaction. The epidemiological evidence linking ultrafine particles with respiratory health effects is still limited and controversial. In the current issue of *Thorax*, Halonen and colleagues⁴ provide new and compelling evidence on the respiratory effects of particles of various sizes that will certainly stimulate further research (*see page 635*).

Different sized particles were measured daily in Helsinki over a period of 7 years, and a source apportionment method was applied to separate the PM_{2.5} fraction from four sources (traffic, long range transport, soil and road dust, and coal/oil combustion). Daily counts of asthma emergency room visits among children, and asthma/chronic obstructive pulmonary disease (COPD) emergency room visits among adults and the elderly were collected. After careful control for time varying confounding factors, ultrafine particles, CO and NO₂ were strongly associated with asthma in children with a delay of 3–5 days. In contrast, asthma and COPD in the elderly were clearly associated with larger particles (accumulation mode, PM_{2.5}, coarse particles), and

CO and NO₂ at immediate lag (same day). Traffic related particles had a strong delayed effect on children's emergency room visits for asthma whereas traffic related and long range transported particles had an immediate effect on asthma/COPD visits of the elderly.

There are several strengths of the paper: a new approach to study the effect of air pollution that combines specificity in the exposure assessment (daily measurements with a differential mobility particle sizer), consideration of the pollution sources and specificity in the age groups corresponding to different respiratory conditions. The authors also give interesting indications for understanding the toxicology of particulate matter. Two aspects need to be discussed in light of the differences between asthma and COPD regarding their baseline obstructive and inflammatory characteristics: the timing of the effects that characterise the response to air pollutants in patients with asthma and in COPD patients, and the difference in the size of the particles eliciting the effects.

Childhood asthma is characterised by reversible airflow obstruction, bronchial hyperresponsiveness and an underlying inflammation. The study by Halonen and colleagues⁴ stresses the delayed role of ultrafine particles on this condition. There are other epidemiological observations with similar findings. Two time series studies on emergency room visits or hospitalisations for childhood asthma in the USA⁵ and Copenhagen⁶ support the delayed effect of ultrafine particles. The delayed effects found in these studies, including the Finnish investigation, apparently are at odds with recent

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