Responses to steroids and bronchodilators in COPD in the ISOLDE trial: the fat lady sings on

N J Gross

Two new findings using data from the ISOLDE trial are presented in this issue of Thorax: (1) patients with COPD cannot be separated into discrete corticosteroid responders and non-responders, and (2) the response of an individual patient with COPD to a bronchodilator challenge on a single occasion does not predict whether or not the patient will benefit subsequently from that agent. Consistency is needed between North America and Europe as to the diagnosis of COPD and the criteria for inclusion in COPD trials.

The main results of the ISOLDE trial have been published and are now part of the canon of knowledge about COPD—inhaled corticosteroids (ICS) do not change the rate of decline of FEV₁ in COPD. This finding is consistent with that of other similar large long term trials, so the question has been settled. As in some of the other studies, there may be decreases in the frequency and severity of acute exacerbations, and quality of life may be modestly improved. These questions are being addressed in separate ongoing long term trials.

Despite the rule that the primary and secondary outcomes of a trial must be prestated and set in stone in the protocol, trials such as ISOLDE are so large and so carefully planned, executed, and monitored that the huge amounts of data they generate offer many opportunities to examine questions other than the prestated outcomes—questions that are scientifically important but which are unlikely ever to find funding as primary outcomes. In the absence of any methodological aspect of the trial that would invalidate it from being used to answer a different question, it is appropriate to mining the data for any and all other useful information they may provide. Sometimes disparaged as “data dredging”, the meticulous review of the data for other insights seems rather to be an economical use of a precious resource—namely, good data which should be exploited for all they are worth. Two important papers in this issue of Thorax illustrate this.

The paper by Burge et al bears on one of the most important remaining issues concerning the long term use of ICS in COPD—is it possible to identify “steroid responders” by a short preliminary course of oral prednisolone? The issue is important because a very large proportion of patients with COPD are already receiving long term ICS, often without a clear rationale or a solid experimental basis; this is a matter of some concern.

Inhaled corticosteroids are probably not innocuous, particularly in the relatively large dosages that are sometimes being used in COPD, and particularly when one considers that ICS may be used continuously for 10 or even 20 years in the COPD population who are older and in whom the common side effects of steroid therapy such as osteoporosis and muscular atrophy are already common. Potential adverse effects of ICS such as these might take many years of continuous use to become evident, and none of the published studies of ICS has exceeded 40 months, which is not nearly long enough to be confident of the safety of their long term use. By the widespread and indiscriminate use of ICS in COPD, might we be making a Faustian compact in which modest short term benefits in some patients are being traded for what may be an epidemic of serious adverse effects over the long term? This possibility, admittedly portrayed in its most disastrous form, makes it most important to determine whether there is an identifiable subgroup of patients with COPD who are not responsive to corticosteroid therapy. If so, these patients should perhaps be saved from even the potential risk of long term ICS use. Previous attempts to identify steroid responder and non-responder groups have been largely unsuccessful, as cited by Burge et al.

The unique design of the ISOLDE study, which included a 2 week trial of oral prednisolone before randomisation into the main 3 year trial, made it possible to address this question with good statistical power. In the present report the authors found no statistical association between the change in FEV₁ resulting from the course of oral prednisolone and any outcome over the subsequent 3 years of treatment with ICS or placebo. This finding invalidates the traditional recommendation that one should perform a steroid trial before instituting ICS on a long term basis. It could be argued that the increase in FEV₁ during the short prednisolone trial might not be an appropriate way to identify responder and non-responder groups. Indeed, the FEV₁ does not seem to be a measurement that correlates well with clinically relevant outcomes. However, it is hard to know what other outcome(s) of a short trial of prednisolone would be better than the FEV₁, or even practical in the clinical setting. If the purpose of a preliminary prednisolone trial is to guide the clinician in his/her decision whether or not to administer ICS to the patient with COPD, the indicator of its success or failure must be one that clinicians can readily apply in their daily practice. This rules out the measurement of markers of COPD-type inflammation in airway secretions, cells, or breath condensates that might conceivably predict steroid non-responsiveness. One day, perhaps, but such assays are neither validated nor realistic in clinical practice at present.

The present trial and all previous evidence seems to suggest, as Burge and colleagues state, that “patients with COPD cannot be separated into . . . corticosteroid responders and non-responders”. Whether this is because there really are no subgroups of steroid responders and non-responders, or whether there are but we have not yet discovered how to identify and differentiate them, is uncertain. I believe the right course is to keep an open mind about the possibility that there may be responder and non-responder subgroups and to continue to seek ways to identify and characterise them, if they exist. Meanwhile, I regretfully agree with the conclusion that corticosteroid trials are not diagnostically helpful in primary care.

The paper by Calverley and colleagues in this issue of Thorax, also based on data from the ISOLDE trial, addresses the important question of whether poor bronchodilator responsiveness is a valid criterion for the diagnosis of COPD or predicts disease progression. Although the ISOLDE population was selective due to the inclusionary criterion of a poor bronchodilator response, Calverley et al show that “classifying patients as ‘bronchodilator responders’ and ‘non-responders’ can be misleading and does not predict disease outcome”.

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The problem surrounding the notion of non-responsiveness to bronchodilators in COPD is the legacy of a document generated by a group of academic lung specialists who met in 1958 to establish diagnostic criteria for chronic obstructive lung diseases. They defined what we now call COPD as “a group of diseases with persistent or irreversible obstructive lung disease”. However, it has been known for as long as spirometry has been routinely performed that this definition is flawed and that patients with clinical features that every practising respiratory physician would call COPD are often capable of a “significant” bronchodilator response. The only thing one can confidently say about the bronchodilator responsiveness of patients with COPD is that it is not, on average, as great as that in patients with asthma. But the overlap between the two diagnoses in this respect is so great that they cannot be reliably distinguished on this basis. Bronchodilator responses of patients with COPD can, in fact, be quite large with some current agents, and patients on the mistaken notion of bronchodilator non-responsiveness that goes back to an era when spirometric tests were very rarely performed.

Two papers, two important messages. Does the fat lady have another encore for us?

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Breathing exercises and asthma

M Thomas

Evidence to support the efficacy of complementary and alternative medicines in asthma is limited. A study of the effect of two breathing exercises (Butekyo and pranayama) in patients with asthma reported in this issue of Thorax contributes to the evidence base, but further controlled studies are needed.

There is considerable lay and professional interest in non-pharmacological treatments for asthma, with reports that up to one third of people with asthma resort to complementary and alternative medicines (CAM). The evidence-based review undertaken for the British guidelines on the management of asthma found the current evidence for the presence or absence of efficacy of many CAM interventions to be inadequate, and further controlled studies are encouraged. Breathing exercises and yoga have been widely used to treat asthma in Eastern and Western societies for many years, and generally centre on manipulating the respiratory pattern to reduce respiratory frequency and hyperventilation. The Butekyo breathing technique, based on the barely tenuous scientific premise that asthma is caused by hyperventilation, makes sweeping claims for effectiveness in asthma. Though little effect on other measures of functional asthma was seen in the Butekyo group, although the magnitude and clinical relevance of the improvement was less clear with the unvalidated scoring tool used. It is still, however, far from clear whether or not breathing exercises can improve asthma outcomes, in which groups they may be effective, or what the mechanism of effect may be. In this issue of Thorax Cooper et al. report a further controlled trial investigating the effectiveness of Butekyo and a device mimicking pranayama yoga exercises, and conclude that the Butekyo method can improve symptoms and reduce bronchodilator use but not by affecting lung function or bronchial hyperresponsiveness.

There is clearly a need for controlled studies on representative patient groups in this area. This study recruited symptomatic adult patients treated with inhaled corticosteroids who had reversible airflow obstruction and hyperresponsiveness to inhaled methacholine. The patients were recruited from an asthma volunteer database and by advertisement, so it is not certain that the study group is necessarily representative of the wider asthma population. The investigators have made efforts to address the real methodological problems that exist in controlling and blinding multifaceted CAM treatments. The study attempted to control for non-specific intervention effects independent of breathing pattern alterations by comparing a variety of asthma outcomes in the Butekyo group with those in the groups using an active and inactive “placebo” pranayama breathing training device. The Butekyo group did, however, receive a higher level of professional contact than the other groups, so it is possible that the effects of professional attention may act as a confounding influence on the improved outcomes reported. Statistically significant improvements in symptom scores were reported for the Butekyo group, although the magnitude and clinical relevance of the improvement was less clear with the unvalidated scoring tool used. Reductions in bronchodilator use were seen in the Butekyo group, although since the Butekyo training process strongly discourages patients from using bronchodilators, the reduction may represent a learning effect and may not be appropriate as a surrogate marker of asthma control in this situation. No differences were seen in other objective outcome measures—including bronchial hyperresponsiveness, lung function, and asthma exacerbations—but there were any differences in the ability to reduce inhaled corticosteroid dosage, although the study may not have been powered adequately to show this.

If subjective benefits are indeed found in relation to Butekyo and other types of breathing retraining, it is necessary to attempt clarification of the mechanisms of improvement. International consensus has defined asthma as an inflammatory condition characterised by airways hyperresponsiveness and variable airflow limitation, and subjective improvements need to be related to objective measures of asthma severity. Asthma is a complex disease and the relationship between objective physiological measures and the patients’ subjective experience of their condition is far from simple. It has, for instance, been shown that psychosocial and emotional factors influence asthma symptoms and asthma related health status independently of asthma severity, and that the relationship between airflow obstruction and symptoms is very weak with some patients experiencing high levels of symptoms in spite of normal or near normal lung function. The question of whether improvements in asthma symptoms associated with breathing retraining may result from indirect effects on emotional or psychological factors cannot be answered from the current evidence. It has been reported that up to 30% of adults with asthma in the community, of all severity levels, may have symptoms suggestive of functional breathing disorders, raising the possibility that symptom improvements following breathing retraining interventions may relate to treatment of a co-existent functional problem rather than of asthma per se. This possibility is strengthened by the results of this study, in which subjective symptom improvements are not matched by changes in objective parameters of airways calibre or hyperresponsiveness. Other studies have, however, shown improvements in bronchial hyperresponsiveness in relation to breathing exercises. No currently published studies have investigated the effects of breathing retraining on parameters of airway inflammation. Preliminary evidence from an animal model suggests that repeated dry air hyperventilation can result in airways inflammation and hyperreactivity, so raising a possible link between abnormal breathing and asthma. It is also unclear whether different types of breathing retraining interventions—such as physiotherapist based programmes for treating hyperventilation, different schools of yoga, and the Butekyo method—have similar effects and act by similar mechanisms.
In spite of the various highly effective inhaled and oral pharmacological options available for the treatment of asthma, the goals of asthma management are not currently being met, with high levels of potentially avoidable morbidity revealed in surveys. For a variety of incompletely understood reasons, many of our patients are unable or unwilling to comply with our recommended treatment, and many wish to explore non-pharmacological treatment avenues such as breathing exercises. In contrast to the wealth of high quality evidence informing pharmacological decision making in asthma, often driven by the pharmaceutical industry, there is a paucity of information for rational decision making in non-pharmacological treatments. Although progress is being made in improving this evidence base, large holes still exist in our knowledge and understanding and further controlled studies are required to confirm effectiveness and clarify mechanisms of benefit if found.

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SARS

Where is SARS now?

P J M Openshaw

The WHO and respective governments must be praised for their incisive and energetic leadership which has greatly limited the impact of SARS, but we can only guess what will happen next winter.

In February 2003 the World Health Organisation (WHO) received alarming news of antibiotic resistant community acquired pneumonia in Vietnam, Hong Kong, and Singapore of apparent viral origin. It named the disease “severe acute respiratory syndrome” (SARS) and issued urgent advice directed at reducing transmission and spread (http://www.who.int/csr/media/sars_wha.pdf). With unprecedented speed, the probable cause was identified as a novel coronavirus, now named SARS CoV. The imposition of draconian public health measures appears to have brought the disease under control, but there is still concern that, with over 8000 suspected or confirmed cases and contact networks reaching millions, there is every prospect that the disease will become endemic in China or spread to areas of the world in which it cannot be contained.

Although co-infection with SARS CoV and another agent has not been ruled out as the cause of SARS (particularly in “superspreaders” causing numerous secondary cases), SARS CoV alone seems likely to be the cause of most cases of SARS and can reproduce the disease in non-human primates. Coronaviruses have the distinction of containing the largest genome of all known RNA viruses. They are widespread throughout the animal kingdom, causing bronchitis (poultry), hepatitis (mice), enteritis (horses and pigs) and peritonitis (cats), but often infecting multiple sites. Known coronaviruses fall into three clades (members of two of which cause about 20% of common colds), but the SARS CoV occupies a new fourth clade of its own. It is clearly a coronavirus, but not closely related to any previously sequenced virus. It presumably arose from an animal source in southern China, perhaps in a species with relatively little contact with man and in which viral infection has been little studied. The civet cat has been proposed as a possible source, but systematic studies of coronaviruses in a wide spectrum of wild and semi-domestic species are not yet complete. RNA viruses tend to evolve rapidly and coronaviruses frequently undergo homologous recombination, so that co-infection with an established human coronavirus and SARS CoV could lead to emergence of new virus species combining various features of the parental strains.

The clinical picture of SARS CoV infection continues to emerge, but patients in the early stages may not complain of respiratory symptoms and my not be febrile; influenza-like symptoms, abdominal pain, and diarrhoea are common, followed by transient high fever and then by ARDS, progressive respiratory failure, spontaneous pneunymoedema, and disseminated intravascular coagulopathy (DIC). Full recovery may take weeks or months. The WHO definitions were established to assist in the definition of hospital cases and have a sensitivity of only 26% in the detection of non-hospitalised patients defined by seroconversion. Particular problems with SARS CoV include:

- the diagnosis is difficult;
- it spreads fast in hospital wards (especially if nebulisers are used or emergency resuscitation is performed);
- even fit, healthy people (including hospital workers) are affected; and
- there are no proven specific treatments.
Lung volume reduction surgery

Closing the NETT on lung volume reduction surgery

P M A Calverley

The National Emphysema Treatment Trial (NETT) of lung volume reduction surgery in patients with COPD has shown that surgery can and should be evaluated on a par with other forms of treatment.

Most textbooks and many physicians now use the term “chronic obstructive pulmonary disease” (COPD) to define airflow obstruction that results from a variable combination of small airways disease and loss of elastic recoil due to emphysema. A detailed knowledge of the underlying pathology does not normally influence the treatment prescribed, with one important exception. Patients who have large space occupying bullae visible on their plain chest radiograph can experience significant improvements in lung function and exercise capacity if these lesions are resected, a treatment that is now well established. Initial attempts to extend this approach to include the resection of gross emphysematous areas of lungs were scorned by physiologists as being irrational and were associated with significant perioperative morbidity and mortality. The pressures of a lengthening lung transplantation waiting list led Cooper and colleagues to revisit this approach using modern techniques of intensive care and better surgical methods of strengthening the previously suspect suture lines between friable areas of lung. Their report of significant improvements in spirometry, breathlessness, and 6-minute walking distance after surgery compared with historical controls had a

Experience with smallpox and polio shows that a highly effective vaccine is essential for global elimination of an infectious disease and that an animal reservoir makes elimination hard or impossible. Vaccine development is a worldwide priority, funded by US Federal support for industrial partners using three distinct approaches. A vaccine would be likely to prevent systemic spread; there are successful vaccines for some veterinary coronavirus infections and it would be possible to test vaccines in non-human primates. However, success is not guaranteed and anti-viral drug therapy can even increase disease severity—for example, in coronavirus induced feline peritonitis. The existing human coronavirus common cold agents are able to re-infect despite low variability, and prolonged viral shedding in SARS patients (about 70% of patients are still positive at day 21 on stool samples) despite good serological responses (60% seroconversion by day 21 and virtually 100% by day 30) indicates that a specific immune response may not be capable of terminating infection.

The SARS outbreak has important lessons for us all. Epidemics of this type do not respect national borders, have a large impact on tourism, trade and travel, and potentially have devastating effects in poor countries with insufficient infrastructure. The unprecedented speed of international and national collaboration undoubtedly contributed greatly to limiting the impact of SARS, and the WHO and respective governments must be praised for their incisive and energetic leadership. What will happen to SARS during the next 6–9 months is guesswork—a major worldwide epidemic might develop this coming winter or the outbreak could die down. Certainly, there will be more outbreaks of respiratory viral disease in the future, and we need to be well prepared for such events.

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Lung volume reduction surgery

The National Emphysema Treatment Trial (NETT) of lung volume reduction surgery in patients with COPD has shown that surgery can and should be evaluated on a par with other forms of treatment.
dramatic effect on thoracic surgical prac-
tice in the USA. Their findings were rep-
licated by others using a variety of surgi-
cal approaches and techniques and were
reported in a series of uncontrolled case
studies7 which suggested variable benefit
when meta-analysed.8 After some de-
bate, this procedure is now known as lung
volume reduction surgery (LVRS). Detailed
physiological testing before and after surgery
showed that there was a significant improve-
ment in resting lung volumes in most cases, together with less
dynamic hyperinflation during exercise and
improved diaphragmatic mechanics sec-
tondary to changes in chest wall
configuration,4 and increased lung elas-
tic recoil in the remaining lung.7 Theo-
retical models were developed to explain
how lung volume reduction could improve
expiratory flow, irrespective of the
distribution of emphysema.9 Proven im-
provement with a later deterioration
was found in FEV1, health status, and the degree of
mortality was 7.9% in those randomised
to surgery compared with 1.9% in those
randomised to medical treatment. In contrast, those with upper lobe predo-
nance of disease and a preserved exercise capacity fared scarcely better
than the high risk group previously
identified. The remaining two groups lay
between these extremes with no benefit
improvement in terms of health status
improvement, spirometry, and exercise
capacity.

The companion report10 examined the
healthcare costs associated with this
treatment which were substantial,
amounting to $190 000 per quality ad-
justed life year (QALY) at 3 years
and $53 000 at 10 years. Unsurprisingly, the
cost effective treatment was di-
rected at those with upper lobe predomi-
nant disease and a low exercise capacity ($98 000 per QALY at 3 years
and $21 000 per QALY at 10 years). The 10
year data, adjusted for the likely survival
in this population, extrapolated the ben-
fits seen at 3 years and assumed that the
treatment differences observed were
maintained over this time—both rather
imponderable issues in patients such as
these. By comparison, coronary artery
bypass surgery costs $64 000 per QALY
gained (2002 prices).

There are many lessons to be learned
from the NETT study. Firstly, important
improvements in exercise capacity and
health status are possible in patients
with severe emphysema by reducing the
operating lung volume at which these
patients breathe. The changes in exercise
capacity and well being can be dramatic
even when the spirometric improvement
is small, an important lesson which is
applicable to all COPD treatments. These
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out an unacceptable mortality risk, at
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future clinical trials and in our clinical
practice. An impaired exercise capacity is
not just a marker of poor prognosis,11 but
also appears to define the patients with
the most to gain from treatment of their
underlying disease. However, we should
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drawn in this study as some of the most
important are based on a post hoc analy-
sis of predictor variables, a source of con-
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prehensive prospective cost effectiveness

 candidacy for LVRS. Following
some debate, LVRS was introduced
into practice. Addressing the cost
effectiveness of the procedure.

The National Emphysema Treatment
Trial (NETT), the results of which were
reported initially as an interim analysis
and which have now
been reported both as an intention to
treat analysis7 and in a companion paper
describing the cost effectiveness of the
procedure.11

Of the 3777 patients screened, 1218
were finally randomised, 580 eventually
remaining after randomisation, four
subgroups emerged. Patients with upper
lobe predominant emphysema and a low
exercise capacity showed the greatest
and best sustained improvements in all
physiological and symptomatic variables
and also had a significantly better survival experience than similar patients
randomised to medical treatment. In
contrast, those with lower lobe predo-
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analysis also emphasizes the economic impact of advanced COPD and the need to offer surgery only to those patients in whom the benefit can be best justified, given the scarcity of healthcare resources.

Future analysis of this important dataset is likely to provide many new insights and to generate further hypotheses that will need to be tested. Perhaps most importantly of all, the conduct of the NETT study has shown that surgery can and should be evaluated on a par with other forms of treatment. Only when this is done can we be certain that our intervention as doctors helps rather than harms our patients.

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LUNG ALERT

A new test for latent tuberculosis infection?


This study compared the enzyme linked immunospot assay (ELISPOT) with tuberculin skin testing (TST) for the diagnosis of latent tuberculosis infection (LTBI) in low prevalence settings. The ELISPOT assay measures interferon gamma secretion by blood mononuclear cells to ESAT-6, an antigen present in Mycobacterium tuberculosis but not in M bovis or environmental mycobacteria. 535 students were tested in a large tuberculosis outbreak in a UK school. Although agreement between the tests was high (89%), ELISPOT correlated significantly more closely with M tuberculosis exposure than did TST based on duration of exposure (p=0.007) and measures of proximity to the single index case (p=0.002). TST was significantly more likely to be positive in BCG vaccinated than in non-vaccinated students. The authors conclude that ELISPOT offers a more accurate approach than TST for the identification of patients with LTBI, and is more precise at targeting preventative treatment.

Interpretation of studies in this area is difficult because of the lack of a gold standard for diagnosing LTBI. There are no comparative studies between ELISPOT and QuantiFERON, an existing assay which measures the interferon response to PPD in whole blood. Although the TST requires a return visit for interpretation, it does not require phlebotomy, analysis within a few hours, laboratory expertise, or expensive equipment like an ELISPOT reader. Studies are required to assess the cost/benefit ratio of ELISPOT and its positive predictive value for the subsequent development of tuberculosis.

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